RENAL DISEASES

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with 123 Illustrations and 4 Color Plates



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PREFACE TO THE SECOND EDITION

No changes have been made in the basic plan of the monograph but since about 18 000 additional autopsies have been surveyed a larger group of cases of each disease is available for study The chapters on tubular diseases and extrarenal azotemia have been enlarged The recent additions to the literature have been incorporated into the text

F T B

PREFACE TO THE FIRST EDITION

This monograph is in part a compilation of studies on renal diseases carried on by the author during the past twenty five years but a large amount of new material is included The structural changes in the kidneys the pathological physiology and the clinical manifestations of each disease are discussed The rationale of treatment is presented but the reader is referred to special papers for the details of therapy The relation of hypertension to the kidneys is discussed fully and there is a discussion of the toxemias of pregnancy and the renal lesions in diabetes In the exposition of each renal disease an effort is made to correlate the structural changes with the clinical manifestations The pathologist often cannot make an accurate diagnosis unless he knows the clinical symptoms and the clinician may be misled if he ignores the anatomical background of the disease It is hoped that this monograph will help to bring about closer cooperation between these two groups of investigators

The photographs were made by Mr Henry Morris

F T B

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CHAPTER VIII

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RENAL DISEASES

CHAPTER I

INTRODUCTION. CLASSIFICATION OF RENAL DISEASES

THE purpose of this monograph is to present the pathology of the various renal diseases and the features by which they may be recognized clinically and at postmortem. The pathological physiology is discussed in connection with each disease since the type of functional disturbance is usually closely related to the underlying structural alterations in the kidneys.

The literature of renal diseases is now so voluminous that one can survey only the more important contributions and indicate the stages through which our thinking has progressed. Abundant references are cited for those who desire more complete information.

Renal diseases are more easily understood when classified on an anatomical basis. Apart from the malformations and hydronephrosis we may distinguish (*a*) glomerular diseases, (*b*) tubular diseases, (*c*) diseases of the interstitial tissue, and (*d*) diseases of the blood vascular system. The functional disturbances correspond rather closely to the anatomical changes brought about by disease. The diseases will be discussed according to the following outline:

CLASSIFICATION OF RENAL DISEASES

I. Malformations
- A. Renal agenesis
  - 1. Bilateral
  - 2. Unilateral
- B. Renal hypoplasia
  - 1. Unilateral dwarfed kidney
  - 2. Bilateral hypoplasia
- C. Renal ectopia
- D. Anomalies due to fusion
  - 1. Horseshoe kidneys
  - 2. Unilateral fused kidney: crossed renal ectopia
- E. *Duplication of pelvis and ureter*
- F. Cystic disease of the kidneys
  - 1. Polycystic kidneys
  - 2. Solitary cysts

II. Obstruction of the urinary tract—hydronephrosis

- III Glomerular diseases
  - A Diffuse proliferative glomerulonephritis
    - 1 Acute
      - *Other forms of acute nephritis*
    - 2 Subacute
    - 3 Latent chronic
    - 4 Active chronic
  - B Membranous glomerulonephritis—lipoid nephrosis
  - C Amyloid disease
  - D Toxemias of pregnancy
- IV Tubular diseases
    - 1 From bacterial poisons
    - 2 From chemical poisons
    - 3 From sulfa drugs
    - 4 From blood transfusion
    - 5 From casts
    - 6 Of unknown origin
- V Extrarenal uremia
- VI Diseases of the interstitial tissue (pyelonephritis)
  - A Cortical abscesses
  - B Pyelonephritis *following urinary obstruction*
  - C Pyelonephritis without urinary obstruction
    - 1 Acute
    - 2 Chronic
  - D Specific infections
    - 1 Tuberculosis
    - 2 Syphilis
    - 3 Acute lupus erythematosus
- VII Diseases of the blood vascular system
  - A Passive congestion
  - B Infarction cortical necrosis
  - C Periarteritis nodosa
  - D Arteriosclerosis of the kidneys
  - E Arteriolosclerosis of the kidneys and primary hypertension
  - F Diabetes mellitus
- VIII

    - 3 Renal dwarfism
  - B Disturbances in the metabolism of uric acid
    - 1 Uric acid infarcts
    - 2 Gout nephritis
  - C Renal calculi
- IX Tumors

CHAPTER II

NORMAL HISTOLOGY

In each human kidney there are probably about one million units or nephrons. Each nephron begins in a glomerulus and ends in a collecting tubule. The proximal convoluted tubule is connected through the loop of Henle with the distal convoluted tubule which in turn joins a collecting tubule. The different segments of the nephron will be discussed in sequence.



Fig. 1. Section of a glomerulus through its vascular pole. From a case of chronic glomerulonephritis in which shrinkage of the lobules resulting from the disease emphasizes the interlobular fissures. Photomicrograph.

THE GLOMERULUS

The afferent glomerular arteriole at its entrance into the glomerulus divides into several branches which break up into capillaries to

form the glomerular lobules. In mid central sections through the vascular pole one usually sees three or four major lobules united centrally by narrow pedicles and terminating peripherally in broad expansions. The major lobules are separated by deep fissures as shown in Figure 1 and they exhibit a shallow superficial separation into secondary lobules. In normal glomeruli the lobules fit closely together and are not readily seen but in the early stages of atrophy from chronic glomerulonephritis they are separated and easily visible (Fig 1). The fissures between the primary and secondary lobules are lined by glomerular epithelium which covers all the free

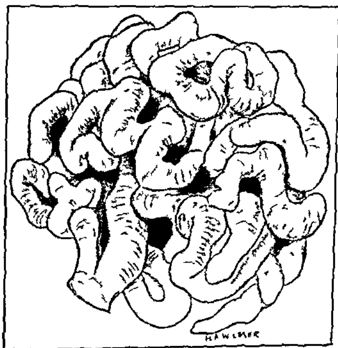


Fig. 2. Drawing of an injected glomerulus (Wilmer). Note the tortuous capillaries without lateral anastomoses.

surfaces of the glomerulus. In wax reconstruction it is seen that *the major lobules are not cone shaped but broad leaf like structures* (Allen).

The deep fissures between the lobules (Fig 1) are evidence that there are no anastomoses between their vessels. Wilmer injected glomeruli with a celloidin mixture and was able to follow the capillaries throughout their course (Fig 2). He found that the capillaries are long winding loops without lateral anastomoses connecting the afferent to the efferent arteriole. This conception was originated by Vimtrup but not so clearly demonstrated.

In each secondary lobule one usually sees two or three capillaries surrounded and embedded in the glomerular epithelium Each capillary consists of a basement membrane lined by an incomplete endothelial layer, and covered on all sides by the protoplasm of

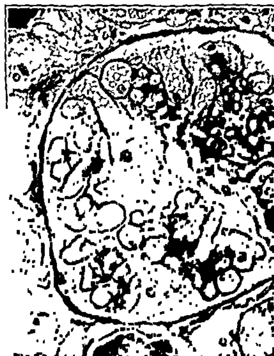
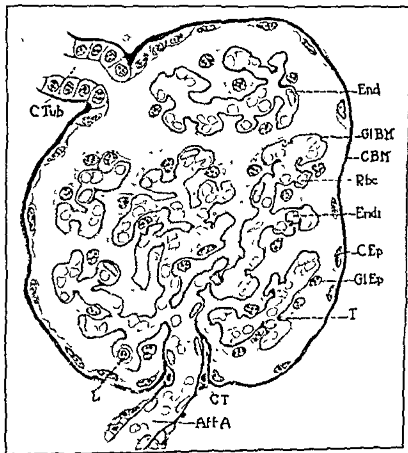


Fig 3 —Normal glomerulus with distended capillaries Mallory Heidenhain stain Photomicrograph

glomerular epithelial cells (Figs 4 and 5) The inner or deep

changes in capillary basement membranes

The structure of the glomerulus is ideally adapted to filtration. The numerous secondary lobules provide a large amount of surface for filtration and the capillaries are all close to the surface. Filtration can occur only through the outer surfaces of the capillaries and not from their deep inner surfaces. The delicate membrane which



[illegible] afferent arteriole

Path.)

separates the blood from the capsular space serves the purposes of filtration well, but trivial injuries may impair its function so that it

[illegible] ortem the majority of the [illegible] empty of blood, and the

same condition obtains in animals unless the capillaries are distended by special means just before the animal is killed. This feature is due in part to the fact that only about one-third of the glomerular capillaries are open and active at any one time under normal conditions but this does not seem to be a complete explanation one must believe that the capillaries commonly contract after death and force out the blood. The finer structure of the glomerulus is best studied when the capillaries are moderately distended in empty collapsed capillaries the basement membrane is wrinkled and one is apt to overestimate its thickness. It is also more difficult to see the endothelial nuclei and intercapillary structures when the capillary walls are collapsed. Sections should not be more than 5 microns thick.



Fig. 5. A secondary glomerular lobule under high magnification. Mallory Heidenhain stain. Photomicrograph. Note epithelial cell between the capillaries. *ep* Nuclei of epithelial cell. *e* erythrocyte. *b m* capillary basement membrane. *p* protoplasm of epithelial cell.

The Glomerular Epithelium.—This layer of cells covers all the free surfaces of the glomerular tuft lining all the interlobular fissures. It is closely applied to the external surfaces of the capillaries fills all the shallow superficial grooves between them and covers their internal surfaces where they are not in actual contact (Figs. 4 and 5. [illegible]

epithelial layer appears to be a syncytium but cell boundaries are sometimes demonstrable (McGregor Bensley). Nuclei are seen at irregular intervals and some of them are in the lobule between the

capillaries Mollendorff regards the epithelial cells as pericytes comparable to the Rouget cells of other capillaries but their origin

mentioned

The Capsular Epithelium —The *glomerular epithelium is continuous at the vascular pole with the capsular epithelium which lines the outer wall of the capsular space* The capsular epithelium consists of flattened cells which at the tubular pole become larger and merge with the cells of the convoluted tubule Unlike the

flammatory

al cells also

page 199)

In the male mouse the capsular epithelium is normally composed of tall columnar cells and Eisen described a kidney from a woman fifty four years of age in which the capsular epithelium had a similar structure

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easily

little

dently do not form a continuous layer since no intercellular boundaries are demonstrable by silver staining except in the main branches of the afferent glomerular arteriole (Bensley) In this respect *glomerular capillaries are unlike all other capillaries*

A few investigators (Borst Wilbur) maintain that endothelial nuclei outnumber the epithelial but my observations do not support this contention In 107 kidneys obtained from persons dead of accidental causes who had previously been in good health 84 per cent *showed only a few endothelial nuclei as in Figures 3 to 5* 15 per cent showed about an equal number of epithelial and endothelial nuclei and only 1 per cent showed a preponderance of endothelial nuclei (Bell 1936) However if one does not select the normals carefully and uses cases in which death was due to an *infectious process the endothelial cells will frequently outnumber* the epithelial since they respond quickly to stimulation by infectious agents (see page 160) Unless the tissue is fresh and well fixed the

epithelial cells are easily lost through desquamation In general endothelial cells are less numerous in children than in adults

The endothelial cells do not act as phagocytes. Under normal conditions the cytoplasm is too scanty for this function When bacteria or carbon particles are injected into the blood stream some particles may be found in the glomerular capillaries but these are either in the bodies of leukocytes or they are merely adherent to the capillary wall No phagocytic action has been demonstrated even for the large endothelial cells of acute glomerulonephritis

The capillary endothelium plays a very important role in disease In intracapillary glomerulonephritis the cells increase greatly in size and number and may obstruct the capillaries completely

The Capillary Basement Membrane —This structure received very little attention prior to McGregor s study in 1929 although it had been previously demonstrated by Ohmori With routine stains it cannot be seen satisfactorily but it is colored a brilliant blue by the Mallory-Heidenhain stain after fixation in Zenker s or Helly s fluid (Fig 5) The basement membrane may also be stained a bright red color by treatment with periodic acid followed by Schiff s reagent (McManus) The demonstration of the basement membrane is indispensable for finer glomerular study since it gives a sharp separation between intra and extracapillary structures

Like the endothelium the basement membrane may react to injury or show changes as a result of injury In acute glomerulonephritis the deep layer thickens and breaks up into small segments which later fuse to form solid masses between the capillaries (Plates I and II) In lipoid nephrosis there is a diffuse uniform thickening of all parts of the membrane (Plate III) It is not clear whether these alterations are a reactive or a degenerative process but they result in disturbances of renal function

The basement membrane is the main part of the normal capillary wall It is a fibrous structure presumably much stronger than the thin layer of epithelial protoplasm the endothelial layer gives only insignificant strength to the capillary

The Juxtaglomerular Bodies A juxtaglomerular body is a group of modified smooth muscle cells (epithelioid cells) in the media of the afferent arteriole just before it enters the glomerulus (Fig 6) Goormaghtigh suggested that they serve to regulate the flow of blood

hypertrophy and hyperplasia of these cells only in cases of extreme renal atrophy produced by arterial constriction (Goldblatt hypertension) The juxtaglomerular bodies are not prominent in normal human kidneys nor in the kidneys of chronic hypertension with chronic uremia but in primary hypertension with acute uremia they

are often conspicuous and some of the epithelioid cells may be granulated (Des Prez)

The Glomerular Arterioles.—The afferent glomerular arteriole breaks up into the glomerular capillaries which are reunited to form the efferent arteriole The efferent vessel is somewhat smaller than the afferent since about 10 per cent of the volume of the blood is lost by filtration in the glomerular capillaries Contraction of the afferent



Fig 6 A juxtaglomerular body From a patient dead of primary hypertension with acute uremia The juxtaglomerular body occupies the media of the afferent arteriole adjacent to the glomerulus

plasma filtered through the capillaries varies directly with the intracapillary blood pressure, it follows that the filtration fraction may be maintained at a normal or increased level by contraction of the efferent arteriole when the renal blood flow is reduced

THE TUBULES

In reconstructions it is seen that the proximal convoluted tubule is quantitatively much more important than the distal (Fig 7) In

cubical cells with relatively clear cytoplasm containing only a few granules, and showing no definite inner striated border A rather striking difference between the two segments is that there are two or three times as many nuclei shown in cross-section in a distal than in

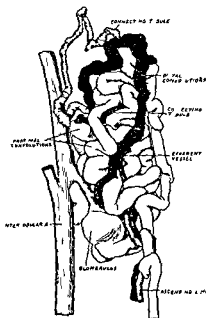


Fig 7 —Reconstruction showing proximal and distal convoluted tubules (Oliver, courtesy of Arch Path)

a proximal tubule (Fig 8) The more complex structure of the proximal segment suggests a more intricate function than that of the distal

There is no satisfactory evidence that the histological structure of the tubule varies under physiological conditions Sauer found that

pinched off to lie free in the lumen as spherical bodies During the excretion of granuloid the ciliated border disappears Lanscano-Gonzalez supports Kosugi's interpretation, but thinks granuloid varies in appearance with different fixatives The view that the spherical bodies are excreted by the cells is also supported by Kruger (1937)

It is rather well-established, however, that "granuloid" is an artefact The lumens of the proximal convoluted tubules frequently



Fig 8 —Normal kidney showing proximal and distal convoluted tubules The proximal tubule is dark and granular and shows a ciliated border the distal tubule is relatively light and contains more nuclei Photomicrograph

contain a variable number of spherical bodies, sometimes very clear, sometimes granular and rarely of solid structure (Fig 8) These bodies are frequently found in the capsular spaces also, and [illegible] that they are not derived from the tubular [illegible] much more numerous in [illegible] kidney is fixed by intra[illegible] have taken place, the [illegible] sharply

separated from the cells and the striated border is intact With poor

[illegible]

the urine

My own observations are in agreement with those of Sauer With the possible exception of the sucrose experiment no clear-cut changes in the cells can be ascribed to increase or decrease of functional



Fig 9 Proximal convoluted tubules from a rabbit kidney following intravenous injection of sucrose This severe hydropic change is transitory the cells recover in a short time

activity Helmholz has shown that the cells of the convoluted tubules are markedly altered temporarily by intravenous injections of large amounts of sucrose Following the injection there is a severe polyuria but no albuminuria or other sign of injury to the kidney If the animal be killed during the polyuria the cells of the convoluted tubules are found distended with large vacuoles filled with clear fluid, but the lumens of the tubules are small (Fig 9) The

vacuolization cannot be interpreted as an increased reabsorption of glomerular filtrate since polyuria means a decreased reabsorption of water it probably represents temporary injury of the cytoplasm

Oliver and Lund state that during secretion of neutral red in the frog's kidney the mitochondria are changed from a rod to a granular form

The highly complex structure of the cytoplasm of the cells of the proximal convoluted tubule has been advanced as an argument for tubular secretion but Peters has pointed out that the selective reabsorption of many substances from the tubular urine is also a complex process and is in fact a secretion from the urine to the blood

The loop of Henle connects the proximal and distal convoluted tubules The ascending and descending limbs of the loop are composed of dark granular cells but the loop itself is composed of thin clear flattened cells The loop of Henle is not present in animals that form a hypotonic urine and there is some physiological evidence that a considerable reabsorption of water takes place here

No convincing evidence of a special function of the distal convoluted tubules is available Their simpler histological structure suggests that they are less highly specialized than the proximal tubules They usually escape injury by poisons which destroy the proximal tubules This may mean that the proximal tubules remove the greater part of the water from the glomerular filtrate and that the concentrated poison then injures the epithelium The collecting tubules are merely conducting channels they are lined with clear cells which appear to have no secretory function The fact that uric acid and sulfonamides are precipitated chiefly in the terminal collecting tubules strongly suggests that reabsorption of water takes place throughout the length of the tubule and even in collecting tubules (see page 32)

Interdependence of the Segments of the Nephron—The entire nephron in a human adult is often as much as 4 cm in length It is coiled in a complex manner and the various segments are supplied by capillaries from different sources nevertheless complete obstruction of a glomerulus is followed by atrophy of its entire associated tubule as far as the collecting tubule It has been maintained that tubular atrophy following obstruction of a glomerulus is due to anemia since the blood passes first through the glomerulus and then to the tubule But the efferent arteriole and the intertubular capillaries receive blood from more than one glomerulus and one may trace an atrophic tubule from its hyaline glomerulus through a rich capillary network among normal tubules It is clearly a disuse tubular atrophy the tubule has no work to do when it receives no glomerular filtrate

Similarly when any segment of a tubule is obstructed by a cast or destroyed by an interstitial exudate the entire nephron undergoes disuse atrophy

If either glomerulus or tubule is completely destroyed by disease

no urine is formed by the nephron The secretion of urine involves the action of both glomeruli and tubules

Oliver made numerous dissections of tubules in chronic glomerulonephritis and concluded that a tubule may persist and even undergo hypertrophy when connected with a glomerulus that is largely or completely obliterated He believes that such aglomerular tubules may persist and function I have not dissected out tubules but I have studied many serial sections of kidneys and have always found

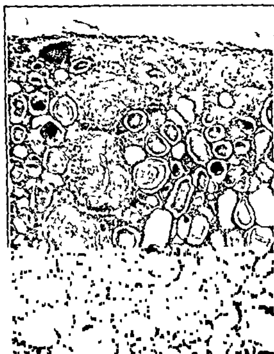


FIG 10 Cortex of a typical unilateral dwarfed kidney Note the thyroid appearance There are no glomeruli but small segments of tubules filled with casts are to be seen Note the thick walled arteries Photomicrograph

a close correspondence between the degree of atrophy of a tubule and the permeability of its glomerulus This relationship is especially clear in subacute glomerulonephritis (Fig 35) in which all the glomeruli are severely obstructed and all the tubules show varying degree [illegible]
rar[illegible]
after o[illegible]
Fig 1[illegible]

After occlusion of a glomerulus tubular atrophy proceeds slowly and does not become prominent until three or four weeks have elapsed In acute glomerulonephritis there is insufficient time for tubular atrophy to occur, but in subacute and chronic forms extensive tubular atrophy is found

In pyelonephritis the tubule is destroyed by the cellular infiltrate, and this also results in atrophy of the entire nephron including its glomerulus

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CHAPTER III

NORMAL AND PATHOLOGICAL PHYSIOLOGY

Early Investigations —Bowman 1842 suggested that the water of the urine is secreted through the glomeruli and the solids through the tubules *He based his theory entirely on anatomical considerations* noting that the structures are especially adapted to such functions

Ludwig 1844 originated the idea that the glomerulus is a simple filter which under the force of the capillary blood pressure allows *all the constituents of the urine to pass through except the proteins* Urine is formed from this filtrate by concentration the water diffusing back through the tubules *Later he realized that urine is not* deproteinized concentrated plasma since the various constituents are not present in the same proportions as in plasma and he therefore modified his theory *to admit the back-diffusion of some solids* along with the water

Heidenhain 1874 maintained that blood pressure is not important in the secretion of urine that the glomeruli secrete water chiefly and that the tubules secrete most of the solids with a minimum of water After section of the spinal cord which lowers the blood pressure so that no urine is formed he found that indigo carmine injected intravenously appears in the cells and lumina of the tubules but not in the capsular spaces An increase of venous pressure does not cause an increased flow of urine The Bowman Heidenhain theory was supported by Nussbaum s classical experiment in 1878 Nussbaum made use of the fact that the glomeruli in the frog s kidney are supplied by the renal artery and the tubules by the renal portal vein After ligature of the arteries no urine is formed but when indigo carmine is injected into the portal vein of a frog with ligatured arteries the dye appears in the tubules If urea is injected similarly urine is formed Nussbaum believed that the tubules excrete indigo carmine and urea and that under the stimulation of urea they excrete water also

Heidenhain s theory prevailed for many years but it was gradually learned that all the observations on which it is based could be explained otherwise It was shown that indigo carmine is visible in the capsular spaces when large amounts are injected (v Sobieranski 1895) It is dilute in the capsular spaces and concentrated in the tubules Section of the spinal cord lowers the blood pressure and reduces the amount of the glomerular filtrate to such an extent that it is all reabsorbed in the tubules and no urine enters the renal pelvis but it does not stop glomerular activity entirely

As regards the Nussbaum experiment Adami in 1885 showed that the collateral circulation is sometimes so well developed in healthy vigorous frogs that ligature of the arteries often causes only temporary anuria. Bainbridge, 1913 1914 showed that when the renal portal vein of the frog was perfused at a pressure of 10 to 12 cm H_2O the perfusion fluid seldom entered the glomeruli and no urine was formed but at a pressure of 35 cm H_2O it did enter the glomeruli and urine was produced. He concluded that the urine was of glomerular origin. Richards and Walker, 1926 confirmed the observations of Bainbridge and showed also that when the renal portal vein is perfused with India ink at pressures even as low as 10 to 12 cm H_2O from 20 to 67 per cent of the glomeruli contain deposits of ink. The collateral circulation in the frog's kidney is such that an independent action of tubules and glomeruli cannot be obtained. There is no fact in the Nussbaum experiment that cannot be explained on the filtration reabsorption hypothesis.

Cushny in 1917 modified and elaborated the filtration reabsorption hypothesis. He believed that the glomeruli filter a fluid which is identical with blood plasma except for the absence of proteins which are held back by the capillary walls. The tubules reabsorb a fluid which varies quantitatively under different circumstances but has a constant composition. The substances present in the reabsorbed fluid are called threshold bodies of which sodium chloride and glucose are examples. Even threshold bodies are excreted in the urine when present in the plasma in excessive amount. The majority of the substances present in the urine are not reabsorbed and are called non threshold bodies. According to Cushny's theory all non threshold bodies should be concentrated to the same extent in the urine but it has been learned that each substance has a different index of concentration. The index of concentration of a substance is its percentage in the urine divided by its percentage in the blood.

The first direct evidence in support of the filtration reabsorption hypothesis was furnished by Richards who together with Wearn devised a capillary pipette for collecting glomerular filtrate directly from the capsular space of the frog's kidney. Only small quantities of glomerular filtrate were obtained but by ingenious chemical methods Richards demonstrated that glomerular urine is a protein free filtrate of the plasma. It contains chloride glucose and urea but no protein. The bladder urine of the frog contains no chloride or glucose showing that these substances have been reabsorbed. The quantity of glomerular urine is greatly in excess of bladder urine indicating that a large proportion of the water is reabsorbed. After injection indigo carmine and phenol red are present in glomerular urine and are therefore excreted at least in part by the glomeruli. Richards has presented convincing evidence that glomerular urine is a dilute fluid containing many substances in about the same

concentration as in the plasma and that water sodium chloride and glucose are reabsorbed by the tubules

At present the prevailing opinion is that the glomeruli filter a fluid into the capsular spaces which is identical with blood plasma in composition except for the absence of protein and certain lipids The glomerular filtrate ordinarily about 100 times as great quantitatively as the definitive urine passes into the tubules where a very large proportion of the water is reabsorbed together with various substances in solution notably glucose chloride and amino-acids A rather large proportion of the filtered urea diffuses back into the blood In man creatinine is secreted partly by the tubules but tubular secretion has not been demonstrated for any other substance normally present in the plasma in animals with glomerular kidneys

The Glomerular Filtrate —It is now believed that glomerular filtration is most accurately measured by the excretion of inulin Inulin is a carbohydrate of high molecular weight Richards has shown that it is present in glomerular urine in the same concentration as in the plasma It is not excreted at all by aglomerular kidneys and its excretion is not affected by phlorizin which inhibits tubular secretion The inulin clearance is independent of its plasma concentration and of the diuresis under all ordinary rates of urine flow and there is therefore no evidence that it is either secreted or reabsorbed by the tubules or that it diffuses back into the blood The inulin clearance is widely accepted as the best measure of glomerular filtration

Based upon the inulin clearance it has been calculated that the average rate of glomerular filtration in man is about 120 cc per minute or 170 liters per twenty four hour period The amount of glomerular filtrate per minute is calculated by multiplying the number of cubic centimeters of urine per minute by the inulin U P ratio The U/P ratio of a substance is its concentration in the urine divided by its concentration in the plasma At low urine flows induced by deprivation of water glomerular filtration is probably decreased and at high urine flows induced by drinking large quantities of water it is presumably increased

Homer Smith found the average renal blood flow in man as measured by the diodrast clearance to be 1300 cc per minute about one-fifth of the cardiac output per minute Of this 1300 cc of blood p
an 770 cc
is filtered

arteriole is definitely less than that of the afferent vessel indicating that less blood leaves the glomerulus than enters it

The formation of the glomerular filtrate is a purely physical process the energy being furnished by the heart which maintains the capillary blood pressure it does not involve any work on the part of the kidney It is a process of ultrafiltration all the constituents of the plasma except the proteins and some lipids pass through the capillary walls We may suppose that the proteins are held back because the pores of the membrane are too small for their passage Richards found that the capillaries of the frog's glomerulus allow the passage of the molecules of egg albumin but not those of horse serum albumin This would indicate a size of the pores in the capillary wall between 4 $\mu\mu$ and 6 $\mu\mu$

Factors Which Influence the Quantity of the Glomerular Filtrate —(*a*) **Blood Pressure** —The most important factor in the formation of the glomerular filtrate is the blood pressure in the glomerular capillaries which is much higher than in capillaries elsewhere because of their nearness to the arteries The glomerular capillary pressure is believed to be 45 mm Hg or higher The colloid osmotic pressure is about 22 mm Hg and therefore the capillary blood pressure must be well above this level

Upon section of the spinal cord of an animal the systolic arterial blood pressure falls to about 40 mm Hg and the formation of urine ceases In man especially during surgical or traumatic shock the blood pressure may fall so low that no urine is excreted When ever the systolic blood pressure is below 70 mm Hg there is usually oliguria or anuria There is evidence that when the capillary blood pressure is low but still above the colloid osmotic pressure a reduced amount of glomerular filtrate is formed and all or most of it is reabsorbed

In perfusion experiments of the kidney Richards demonstrated that an increase of pressure in the glomerular capillaries causes an increased output of urine and *vice versa* He also demonstrated that minute doses of epinephrine constrict the efferent arteriole raise the capillary blood pressure and increase the urine output while larger doses constrict the afferent arteriole and reduce the output of urine The filtration fraction is the percentage of the plasma filtered through the glomerular capillaries into the capsular space This fraction may be determined by dividing the inulin clearance (CI) by the diodrast clearance (CD) Its normal range is usually given as 0 16 to 0 20 Glomerular capillary blood pressure and hence glomerular filtration may be increased by relaxation of the afferent arteriole or by constriction of the efferent This latter mechanism may increase the filtration fraction and maintain normal filtration when the renal blood flow is moderately reduced Smith believes that this mechanism is operative in many cases of essential hypertension

The amount of glomerular filtrate increases as the systemic blood pressure rises up to the normal level but hypertension does

not bring about increased glomerular filtration probably because increased tonus of the afferent glomerular arterioles prevents undue elevation of the capillary pressure

(*b*) **Colloid Osmotic Pressure** —On theoretical grounds one would expect that a decrease of colloid osmotic pressure would result in increased glomerular filtration but actually there is oliguria in the most important disease in which this occurs *viz* lipoid nephrosis In lipoid nephrosis water accumulates in the intercellular tissues throughout the body and is withheld from the kidneys The effect *is similar to loss of water by vomiting The kidneys do not eliminate* water when the result would be a decrease of blood volume If there be increased glomerular filtration in lipoid nephrosis there must be increased reabsorption of water

Hyperproteinemia occurs in multiple myeloma but there is no effect on diuresis The proteins are chiefly globulins which because of their large molecular size do not increase the colloid osmotic pressure to any great extent

(*c*) **Renal Blood Flow** —In kidneys which are histologically normal *glomerular filtration remains fairly constant under marked variations* of renal blood flow This is believed to be due to the action of the *efferent glomerular arterioles which regulate the pressure in the* glomerular capillaries with reduced blood flow they contract Frequently one finds a normal inulin clearance (glomerular filtration) with reduced diodrast clearance (renal blood flow) However an extreme reduction of renal blood flow as in shock decreases glomerular filtration *Heller and Jacobson demonstrated a marked de*crease of renal plasma flow in cardiac failure A decreased glomerular filtration seems an adequate explanation of the oliguria and azotemia occasionally found in persons with cardiac decompensation

In kidneys with reduced parenchyma there is reduced glomerular filtration and reduced blood flow but the reduction of the filtering surface is the primary disturbance

(*d*) **Denervation of the Kidney** —The kidneys are supplied by sympathetic fibers from the splanchnic and renal nerves which are distributed almost entirely to the musculature of the blood vessels There is good evidence that these nerve fibers correspond to vasomotor fibers elsewhere In 1859 Claude Bernard demonstrated that polyuria results from section of the greater splanchnic nerve Complete denervation requires stripping of the nerves off the renal vessels *Bradford (1889) observed a decreased volume of the kidney following stimulation of the anterior roots of the spinal nerves* In 1908 Burton-Opitz and Lucas using a stromuhr found that

tration of urea. Milliken and Karr (1925) in a similar experiment found that indigo carmine appeared from the denervated kidney thirty to ninety seconds sooner than from its normal mate. The denervated kidney secreted a larger volume of urine with a lower concentration of the dye. Caldwell, Marr and Rowntree (1931) found that denervation of the kidneys of dogs caused them to have a polyuria for about five months, after which time the diuresis returned to normal. It has been supposed that denervation causes relaxation of the renal arteries and arterioles with a resulting increase of blood pressure in the glomerular capillaries and a consequent increase of glomerular filtration. Burton-Opitz and Lucas found an increase of renal blood flow following denervation, but Rhoads and his associates found no increase following denervation of the dog's kidneys. Denervation of human kidneys in primary hypertension does not increase renal blood flow. Possibly the efferent arterioles act independently of the afferent and are not affected by denervation. It appears probable that the polyuria following denervation is due to increased glomerular filtration. The return to a normal diuresis some weeks after sympathectomy is interpreted as due to the establishment of an automatic tonus in the renal vessels.

(e) **Effect of Increased Tonus of the Renal Arterioles.**—It is known that the stimulation of the splanchnic nerve causes suppression of urinary secretion, presumably by producing spastic contraction of the renal arterioles and sharply decreasing the blood pressure in the glomerular capillaries. It appears probable that this mechanism is operative in certain instances of anuria following surgical operations which are often referred to as "reflex" anuria.

Reflex Anuria.—Surgical operations, especially on the ureter, kidney or lower colon sometimes result in anuria of sudden onset. After a few days of anuria diuresis is reestablished and recovery ensues. During the period of anuria the blood urea nitrogen may reach uremic levels (100 mg. or higher) and clinical symptoms of uremia may appear. The anuria is not like that of shock since the blood pressure is normal. It has been suggested that the anuria is due to vasospasm from sympathetic overactivity such as occurs in paralytic ileus. The fact that complete functional recovery occurs rapidly is satisfactory evidence that the disturbance is functional and not organic, but we can only make surmises as to its nature. It is important to remember that surgical intervention is contraindicated. Trueta has presented evidence that the anuria following crushing injuries of the extremities is due to tonic spasm of the renal arteries supplying the cortex of the kidneys. He believes that the blood is shunted from the arteries into the veins at the cortico-medullary junction and does not reach the cortex. Severe anemia of the cortex causes the anuria. It is possible that reflex anuria is due to a similar mechanism (see Crush Syndrome, page 285).

(f) **Effect of the Quantity of Fluid Intake on Glomerular Filtration.**—

After ingestion of large quantities of water the normal kidney reacts with a polyuria and the excessive fluid is excreted in about

tubular resorption since it is known that tubular resorption of water is regulated by the hypophysis (see page 33)

In normal individuals restriction of fluid intake or excessive perspiration results in a decreased diuresis with a urine of high specific gravity Since there is no rise of blood urea we may believe that the mechanism is normal glomerular filtration and increased tubular reabsorption of fluid

When the fluid intake is severly restricted or when a large quan

result in a dangerous decrease of blood volume The specific gravity of the urine is usually much less than one finds from a simple reduction of fluid intake The lower specific gravity in this form of dehydration has not been explained There is evidently some tubular damage since the blood urea may continue to increase after the body has been well hydrated

(g) Effect of Decrease of the Glomerular Capillary Bed This is the most important cause of decreased glomerular filtration Experimental removal of three-fourths or more of the renal parenchyma is followed by azotemia and uremia At least one-third of the glomerular filter must be intact to produce an adequate amount of glomerular filtrate In the advanced stages of chronic glomerulonephritis over 90 per cent of the glomerular circulation may be destroyed The glomerular filtrate may be reduced from the normal of 120 cc per minute to as low as 10 cc per minute

In summary glomerular filtration is determined by the blood pressure in the glomerular capillaries and due to the action of the efferent glomerular arterioles it remains fairly constant at all levels of blood pressure except the low level of shock which causes a decrease A marked decrease of renal blood flow as in cardiac failure may cause decreased glomerular filtration Denervation causes a temporary polyuria which may be due to increased filtration Reflex anuria is possibly due to vasospasm of the renal vessels Diuresis is greatly influenced by the amount of fluid intake and the loss of fluid by extrarenal routes Glomerular filtration is reduced in some forms of extrarenal uremia The most important cause of decreased glomerular filtration in disease is reduction of the number of functioning glomeruli

The Function of the Tubules —Glomerular urine is a protein-

free filtrate of the blood plasma containing all the substances of the plasma in the same proportions except the proteins and some of the lipoids It is over 100 times the volume of bladder urine and contains many substances besides water such as glucose and chloride which must be restored to the circulation It is the chief function of the tubules to restore to the blood most of the water and the solutes which must be retained such as glucose amino-acids and salts

pletely Resorption of water apparently takes place all along the tubule The fact that uric acid precipitates out in the collecting tubules in the so-called uric acid infarcts of infants suggests that resorption may continue even into the collecting tubules Similar evidence that concentration continues into the collecting tubules is afforded by the precipitation of sulfonamide crystals in the collect

ing tubules The formation of casts in the proximal convoluted tubules shows that there is considerable concentration in that segment Dyes introduced into the first segment of the frog s tubule become concentrated there Perhaps the greatest resorption of water occurs in the proximal tubule since a great deal of pressure would be required to force the entire glomerular urine through the loop of Henle and the distal convoluted tubule

Glomerular filtration is carried on by the work of the heart but the tubules perform work since they transfer water from a more concentrated to a less concentrated fluid against osmotic pressure They exercise a selective resorption of the solutes taking more of some than of others For the most part the solutes resorbed are those that are needed in the body glucose amino-acids and salts but a large fraction of the filtered urea is also resorbed The resorption of glucose is complete unless there is hyperglycemia in which case there is more glucose in the glomerular filtrate The failure to

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some of the other so-called threshold bodies is similarly due to a limited rate of tubular resorption the solute being present in excess in the tubular urine

Much more work is required of the kidneys when the protein intake is high than when it is low since the kidneys must excrete more urea and work against a higher osmotic pressure on a high protein diet Oliver has shown that the great increase in weight of the rat kidney on a high protein diet is due to a marked hypertrophy of the proximal convoluted tubules The fact that a low protein diet re-

duces the work of the kidneys has led to the view that nephritis should be treated by reducing the intake of protein (see page 203)

There has been much discussion of the role of the tubules in excretion Marshall and others have shown that the aglomerular tubules of certain teleost fishes excrete a small amount of water and all substances in the plasma except protein and sugar It has been argued therefore that mammalian tubules also have these functions It has been clearly established (Marshall) that phenol red is excreted largely by the tubules and Oliver has shown that neutral red is similarly excreted but there is no convincing evidence that substances normally found in the plasma other than creatinine are excreted by the tubules to any notable degree To deny an important secretory rôle to the tubules is not to underestimate their importance for as Peters* has said so well A process of reabsorption which is so regulated that from an undifferentiated ultra filtrate of serum water and solutes are removed with such discrimination that the end result is the maintenance of a constant internal environment is quite as inexplicable in terms of physics and chemistry as a secretory process that attains the same ends In fact reabsorption is nothing more than a process of secretion directed from the tubules toward the blood stream

Rôle of Hormones —The only hormone known to influence the output of urine is pitressin an extract of the posterior hypophyseal lobe Injections of pitressin tend to decrease diuresis In some cases of diabetes insipidus in which there is an excessive output of urine of low specific gravity the polyuria may be controlled by administration of pitressin This fact supports the belief that pitressin acts upon the tubules to promote resorption of water and in its absence less glomerular filtrate is resorbed However hypophysectomy reduces both diodrast and inulin clearances to about one-half their normal values indicating that both renal blood flow and glomerular filtration are reduced (White and Heinbecker)

The tubules play an important role in protecting the body against acidosis From urea they form ammonia which combines with acids that are to be excreted and thus prevents excessive loss of base from the blood The tubules also synthesize hippuric acid from benzoic

atrophy (see page 383)

Effects of Tubular Injury —In view of the fact that one of the major functions of the tubules is reabsorption of water from the glomerular filtrate one would expect tubular injury to produce polyuria with urine approaching the composition of the glomerular filtrate but

* From Peters Body Water The Exchange of Fluids in Man Courtesy of Charles C Thomas Publisher Springfield Illinois

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there are few clinical or experimental conditions in which this occurs. In diabetes insipidus the capacity of the tubules to absorb water is impaired and there is polyuria with a urine of low specific gravity. In the stage of recovery from sublimate nephritis the regenerated *tubular cells have not yet attained full functional capacity* and are unable to concentrate the glomerular filtrate, the result being a urine of low specific gravity with a normal diuresis. Phloridzin poisoning impairs the capacity of the tubules to excrete creatinine and to reabsorb sugars. In the phloridzinized animal or man the *clearances* of creatinine and sugars approach that of inulin.

In nearly all clinical conditions with severe tubular injury the effect is oliguria or anuria. Apparently all the glomerular filtrate diffuses back through the damaged tubular cells. This topic is discussed more fully under tubular diseases (see page 270).

Excretion of Normal Blood Constituents.—Water.—It is well established that water is eliminated almost entirely through the glomeruli, although in aglomerular kidneys a small amount of water is excreted. *About 99 per cent of the water in the glomerular* filtrate is normally resorbed by the tubules.

Polyuria refers to an excessive amount of urine. Cushny explained that polyuria may be brought about either by increasing glomerular filtration (glomerular diuresis) or by decreasing tubular resorption (tubular diuresis). The chief conditions in which polyuria occurs are: after denervation of the kidneys, diabetes mellitus, diabetes insipidus, chronic renal insufficiency, and after ingestion of large quantities of water.

Polyuria does not imply increased glomerular filtration. In advanced chronic renal disease of several types there may be polyuria with a great decrease of glomerular filtration (low inulin clearance).

It was pointed out above (see page 30) that denervation of the kidneys in dogs causes a transitory polyuria with urine of low specific gravity. It is probably the result of increased glomerular filtration, but the mechanism is in dispute.

In diabetes mellitus the blood plasma and therefore the glomerular filtrate contains an excessive amount of glucose. The tubules can resorb glucose only at a limited rate; it therefore accumulates in the tubules raising the osmotic pressure of the tubular urine and delaying the resorption of water. The result is an excessive amount of urine of high specific gravity due to the high content of sugar. The polyuria is due to *decreased resorption of water*.

In diabetes insipidus there is polyuria with urine of low specific gravity (1.001 to 1.005). It is commonly believed that the increased diuresis is due to lack of the hormone pitressin which promotes tubular resorption of water.

In chronic renal insufficiency there must be *decreased glomerular* filtration because of the marked reduction in the number of func-

tioning nephrons but there is usually a polyuria except with severe insufficiency The urine is of low specific gravity It is commonly assumed that this polyuria is due to rapid passage of the filtrate through the tubules The number of open glomerular capillaries is greatly reduced and these presumably filter at maximum capacity The patient also has a high blood urea which would increase the osmotic pressure of the glomerular filtrate and contribute to the decreased absorption of water by the tubules

The polyuria which follows ingestion of large quantities of water is probably due to decreased tubular resorption brought about by the action of pitressin on the tubules

Oliguria and Anuria — A decreased output of urine may be due to several causes

(*a*) Obstruction in the urinary tract *viz* hypertrophy of the prostate tumors which obstruct the bladder or ureters calculi etc These obvious causes require no discussion

(*b*) Decreased intake of fluid The continuous withholding of water from the body soon causes oliguria and finally results in anuria since the blood will not give up water needed to maintain its volume It is not known whether the decreased diuresis is due to less filtration more resorption or both processes

(*c*) Loss of water through extrarenal routes Excessive perspiration results in a reduced amount of concentrated urine Similarly excessive loss of water in intestinal obstruction from vomiting or from severe diarrhea may cause severe oliguria or even anuria as well as a rise of blood metabolites to uremic levels A massive hemorrhage may also cause suppression of urine and uremia These conditions often referred to as extrarenal uremia are due to dehydration no urine is formed when the loss of fluid would produce a dangerous decrease in blood volume (see page 288)

(*d*) Retention of fluid in the tissues When the colloid osmotic pressure is low as in lipoid nephrosis or when the venous pressure is markedly increased as in decompensated heart lesions water passes from the capillaries into the tissue spaces and the patient becomes edematous Since the fluid accumulates in the tissues it is not presented to the kidneys hence there is a decreased output of urine

(*e*) Tubular lesions On theoretical considerations one would expect tubular lesions to decrease resorption and cause polyuria but the opposite result takes place The best clinical example of a degenerative tubular lesion is found in mercuric chloride poisoning There is at first oliguria and a little later anuria The glomeruli appear normal but the tubules are necrotic In the frog Richards observed that the glomerular circulation is normal and that glomerular filtrate is formed in the usual amount Since no urine reaches the pelvis it is obvious that the glomerular filtrate diffuses back through the necrotic tubular cells into the interstitial tissues Mild injuries of the tubules such as are found in cloudy swelling do

not interfere with their functions Widespread obstruction of the tubules by casts may cause anuria as in uremia following transfusion of incompatible blood and in multiple myeloma

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treated by administration of fluid by any available route In reflex anuria one need only wait until the vascular spasm is relaxed The anuria of acute glomerulonephritis or of corrosive sublimate poisoning is not amenable to direct treatment The anatomical mechanism for elimination of water in the kidneys is temporarily or permanently destroyed The forcing of fluids to such patients sometimes results in death from edema of the lungs One can only try to eliminate fluid by other channels in the hope that the kidneys may gradually recover some of their function

Frequently it is desirable to promote diuresis in order to remove edema fluids In cardiac edema treatment should be directed toward restoring cardiac compensation before diuretics are used since increased venous pressure is the chief cause of the edema In lipoid nephrosis the edema is due to the low level of the plasma proteins and the consequent decrease of their colloid osmotic pressure Regardless of the cause of the edema certain drugs may be helpful in removing it

Diuretics are given to increase the output of water in order to remove accumulations of edema fluid or to promote the elimination of waste products such as urea In theory increased diuresis may be due to increased glomerular filtration or to decreased tubular resorption but the ways in which various drugs promote diuresis have not been determined Diuretics are useful chiefly in the removal of edema fluids from patients who have no serious impairment of renal function such as cardiac edema and the edema of lipoid nephrosis They have little or no value in promoting the elimination of waste products from the blood in renal insufficiency

Ammonium chloride produces acidosis In the liver ammonia is converted into urea leaving the excess free chloride ions in the plasma to be neutralized by bicarbonate or other buffers or to be excreted in the urine combined with ammonia of renal origin The diuresis may be due to increased amounts of ammonium chloride or fixed base in the tubular urine *Urea* is an effective diuretic It is

believed to increase the osmotic pressure of the glomerular filtrate

The *organic mercurials* (salyrgan mercupurin) are the most effective of all diuretics The mechanism by which they produce diuresis has not been determined

Water is a valuable diuretic to use during the administration of sulfonamides to prevent undue concentration of these substances in the tubular or pelvic urine In the presence of renal insufficiency it has little value and may be harmful by causing accumulation of edema fluid There is impairment of the excretion of water in renal insufficiency the forcing of fluids merely causes water to accumulate in the tissues

Urea — Urea is the most important waste product excreted by the kidneys It is a product of protein metabolism and its percentage in the blood varies under normal conditions with the amount of protein assimilated In the normal fasting adult the blood urea nitrogen is 12 to 14 mg per cent (Tileston Wider and Comfort) Above 20 mg per cent is definitely abnormal

The percentage of urea in the urine varies with the diuresis In the glomerular filtrate of the frog Richards found urea in about the same proportion as in the plasma Urea is excreted entirely through the glomeruli in the tubules it is concentrated by reabsorption of water A rather large fraction of the filtered urea is reabsorbed Moller and Van Slyke found the maximum urea clearance in normal persons from 64 to 99 average 75 No increased output of urea was obtained by increasing the urine flow above 2 13 cc per minute—which was called the augmentation limit As the diuresis decreases the urea clearance diminishes At urine flows of less than 2 cc per minute the clearance ranges from 40 to 60—average 54 If we use the inulin clearance as a measure of glomerular filtration this means that about one-third of the filtered urea is reabsorbed at a diuresis of 2 cc per minute or more and at a low diuresis about one-half is reabsorbed

Shannon found no augmentation limit for urea excretion in the dog the urea clearance increases throughout the entire range of urine flows At the maximum flow obtainable (creatinine U/P ratio = 10) 40 per cent of the filtered urea is reabsorbed

It is widely believed that urea is not actively reabsorbed by the tubules but that it passes back by diffusion At low urine flows a larger percentage is reabsorbed because of the slower movement of the urine in the tubules In view of the extensive resorption of urea it seems unnecessary to believe that any urea is excreted by the tubules although this occurs in aglomerular kidneys

Although urea is excreted through the glomeruli its retention in the blood is not a measure of glomerular dysfunction but of the reduction of functioning parenchyma

Renal insufficiency is by no means the only cause of high blood urea A notable rise of blood urea may be found in the following

conditions intestinal obstruction of any type attended with vomiting after severe diarrhea after severe hemorrhage after prolonged low fluid intake The above conditions are all examples of dehydration in some form and they are attended with oliguria or anuria The blood does not give up fluid to the kidneys when the result would be a decrease of blood volume but urea continues to be formed

Other diseases which frequently show a high blood urea are those in which there is extensive destruction of tissue proteins such as the early stages of starvation pneumonia and other severe infections

A convincing elevation of blood urea is not found until over 50

of clinical uremia The urea clearance test is however of great value in the early stages of nephritis (see page 52)

A high blood urea may usually be reduced materially by a low protein diet but this improvement in the blood may not be associated with favorable changes in the clinical symptoms

Uric Acid —Normally the blood contains 2 to 4 mg per cent of uric acid Uric acid is derived from the purins of the food and It is sometimes It is so vari ctical value in the diagnosis of renal disease

Creatinine —Normally the blood contains 1 to 2 mg per cent of creatinine The blood level is not much influenced by diet In renal insufficiency creatinine increases in the blood parallel with urea *A creatinine level of 5 mg per cent indicates severe renal insufficiency*

clearance is a measure of glomerular filtration His creatinine clearance test is based on these assumptions It has been shown that in the dog the rabbit the frog and the sheep the creatinine and inulin clearances are identical indicating that in these animals creatinine is excreted only through the glomeruli But it has been established that in man the creatinine clearance is 30 to 45 per cent higher than the inulin clearance the average ratio being 1 39 (Shannon) As the plasma concentration of creatinine is progressively raised above 10 mg per cent there is a reduction in the creatinine clearance indicating that the tubules cannot excrete creatinine beyond a certain rate In phlorizinized man the creatinine and inulin clearance become identical indicating that injury of the tubules prevent strated that some of man with respect to c

clearance ratio was found to be 1.48 in the orang utan 1.23 in t gibbon and 1.22 in the chimpanzee Phloridzin abolishes the diffe ence between the creatinine and inulin clearances in these animal In the baboon and the macaque however they found no significar differences between the creatinine and inulin clearances

Miller and Winkler concluded that endogenous creatinine in man is excreted entirely through the glomeruli since the clearance is the same as that of inulin Functional tests are usually made after administration of creatinine since the small amount of endogenous creatinine leads to technical errors It seems well established that exogenous creatinine in man is excreted partly by the tubules

Sugar —There is satisfactory evidence that glucose is excreted in the glomeruli and resorbed in the tubules chiefly in the proximal convolutions Richards demonstrated the presence of glucose in the glomerular urine of the frog and its absence in bladder urine All observers are agreed that only traces of sugar are excreted by aglomerular kidneys and that sugar is eliminated entirely through the glomeruli Traces of sugar may be excreted in man in a diuresis produced by drinking large quantities of water the urine passes so rapidly through the tubules that there is not time for complete resorption of the sugar

The polysaccharide inulin is especially adapted for the study of glomerular filtration It has a very large molecule (molecular weight 5000) and a very high concentration index which is largely independent of the diuresis Unlike urea inulin clearance is the same at all ordinary rates of urine flow It is generally believed that inulin is excreted only by the glomeruli and there is strong evidence that none of it is resorbed

After injection of the glucoside phloridzin the normal kidney of man and laboratory animals excretes sugar This test was formerly used to estimate the functional impairment of the kidneys, absence of glycosuria indicating a high degree of renal insufficiency In the frog after phloridzin poisoning Richards found that the glomerular filtrate contained glucose in the same proportion as in the plasma but in its passage through the proximal convolution the glucose concentration of the urine increased instead of decreasing as in the normal Therefore phloridzin acts upon the tubule in such a way as to interfere with the resorption of sugar After phloridzin poisoning in dogs and rabbits the concentration ratio of glucose is the same as that of inulin and creatinine indicating that no glucose is resorbed

Why does the diseased kidney fail to excrete glucose during phloridzin poisoning? When a diabetic develops renal insufficiency glycosuria diminishes and a diabetic with one severely diseased kidney excretes sugar only from the normal kidney This is readily understood since a badly damaged kidney has difficulty in excreting solutes of any kind It excretes a reduced amount of urine of low

specific gravity containing only small quantities of solutes The chief reason why no glucose appears in the urine is that relatively little passes through the glomeruli

Phloridzin injures the tubules in such a way that they are temporarily unable either to absorb glucose or to excrete creatinine The ability to reabsorb water is not disturbed

In true renal diabetes there is no hyperglycemia the tubules apparently being unable to resorb sugar although no anatomical damage is demonstrable Because of the elimination of sugar a tubular diuresis occurs as in diabetes mellitus

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riz that the tubules can resorb sugar only at a certain rate and therefore when the tubular urine contains excessive amounts of sugar much of it is excreted in the urine Perhaps this explanation applies to the excretion of other threshold bodies

Neither glycosuria nor hyperglycemia has any relation to renal disease

Phosphates —The phosphates are apparently excreted through the glomeruli In renal insufficiency their increase in the blood parallels that of urea However the phosphate level in the blood is *not as accurate a measure of renal function as the urea level since it is* more influenced by diet

The increase of phosphorus in the blood in renal disease often causes a decrease of the plasma calcium In severe renal insufficiency of long duration (such as polycystic renal disease) the bones may show extensive rarefaction and parathyroid hyperplasia may develop The tetany sometimes observed in uremia is due to low blood calcium

Chlorides —Chlorides are present in the glomerular filtrate in the same concentration as in the plasma and they are partly reabsorbed by the tubules Chlorides do not increase in the blood in renal insufficiency they diffuse so readily that any excess such as occurs after administration of large amounts of sodium chloride passes over into the tissue fluids Apparently the tubular reabsorption of sodium chloride is influenced by *adrenal cortical hormone* since

ABNORMAL URINARY CONSTITUENTS

Proteinuria —The amount of protein in normal urine is too small to be detected by routine laboratory tests Proteinuria usually

called albuminuria occurs in a wide range of diseases and while it always indicates some injury to the kidney it by no means establishes the presence of serious renal disease. Benign albuminuria is much more frequent than true nephritis.

The protein in the urine is largely serum albumin. Hiller, McIntosh and Van Slyke found the ratio of albumin to globulin in the urine above 10 in nephrosis, between 5 and 10 in acute nephritis and usually below 5 in advanced chronic glomerulonephritis. In one case of amyloid disease the ratio was 1.5.

Much discussion has centered about the identity of serum proteins with urinary proteins. One group of investigators maintains that the serum proteins are altered in some way and then excreted as foreign proteins because of this change. Epstein, an advocate of this theory, writes of lipoid nephrosis as albuminuric diabetes. Andrews, Thomas and Welker believe that peptone accumulates in the blood of nephritics and that various poisonous products combine with the serum proteins, altering their constitution and causing them to be excreted as foreign proteins. They regard albuminuria as a detoxifying mechanism.

But the evidence is very strong that albuminuria depends upon injury of the glomerular capillaries and not upon alterations of the serum proteins. In unilateral renal disease albumin escapes through the diseased kidney and not through the normal one. If one kidney of an animal be injured by temporary clamping of its artery, albumin is passed through the injured kidney only. It cannot be maintained that these examples of albuminuria are due to alterations of the serum proteins.

The view that foreign proteins are excreted merely because they are foreign to the body is incorrect. Kerridge and Bayliss perfused the dog's kidney with blood to which various proteins dissolved in 0.9 per cent sodium chloride were added. They found that proteins with smaller molecular weights were excreted, *e. g.*, egg albumin and Bence-Jones protein, while those with larger molecular weights were retained, *e. g.*, serum albumin, serum globulin, gelatin, egg casein. They concluded that proteins are excreted or retained in accordance with the physical size of their molecules and not according to their chemical constitution or biological origin. Richards found that the frog's glomerular capillaries were permeable to egg albumin but not to the large molecules of horse serum albumin. It appears therefore that a very important factor influencing the excretion of a protein in the blood is the size of its molecules.

Hayman and Bender injected 50 to 190 cc. of citrated plasma from nephritics with heavy albuminuria into three persons with normal kidneys. No albuminuria resulted.

Rusznyak and Nemeth perfused dog kidneys with Ringer's solution to which human blood from a case of nephrosis had been added. No albumin appeared in the urine, but when they added sodium oleate to lower surface tension albumin appeared. Upon addition of

calcium chloride the membrane no longer allowed albumin to pass through.

Hewitt found that urinary proteins have the same optical rotatory powers as corresponding serum proteins.

Apart from certain cases of lipoid nephrosis in children there is anatomical evidence of injury of the glomerular capillaries in most instances of heavy albuminuria.

The evidence seems convincing that the escape of serum proteins into the urine depends upon alterations in the glomerular filter and not upon changes in the proteins.

There is no longer any doubt that the serum proteins escape through the glomerular capillaries and not through the tubules. As early as 1879 Runeberg insisted upon this interpretation. One of the first arguments advanced in support of this view was the demonstration of precipitated protein in the capsular spaces. Bieter has shown that the aglomerular kidney does not excrete protein even after it has been poisoned with mercuric chloride.

The Reabsorption of Protein by the Tubules.—Richards stated if any protein is present in the glomerular filtrate of the frog the amount is less than 30 mg per cent. He could not detect quantities less than that amount. It is therefore theoretically possible that some protein passes the glomerular filter and is reabsorbed by the tubules. Whipple demonstrated that there is a little leakage of hemoglobin into the urine when the plasma level is above 100 mg per cent. The actual leakage is only 2 to 3 per cent of the amount in the plasma. Dock and associates found that when trypan blue or Evans blue is absorbed to protein and injected intraperitoneally into normal rats practically no blue granules appear in the tubules but if rats with severe proteinuria be similarly injected the urine becomes blue and numerous blue granules appear in the proximal tubules. These experiments suggest that some protein may escape through normal glomeruli and be reabsorbed by the proximal tubules. However, there has been no measurement of the amount of tubular reabsorption and there is no evidence that it is quantitatively important. In cases of severe proteinuria the amount of protein in the glomerular filtrate is often so great that it can be seen as a homogeneous precipitate in the capsular spaces in microscopic sections. This is strong evidence that the leakage of protein through the glomerular capillaries is the chief cause of proteinuria and that the failure of tubular reabsorption of protein is of little or no consequence. Furthermore, in most instances of severe proteinuria there are demonstrable lesions in the glomerular capillaries and no convincing tubular lesions.

Benign Albuminuria.—Some injury of the walls of the glomerular capillaries is necessary before albumin can escape but very trivial and transitory lesions may result in albuminuria. In 1877 von Leube reported that 4 per cent of 110 presumably healthy soldiers had

albuminuria and that 16 per cent showed albumin when the tests were made after a march. He called this condition physiological albuminuria. Since 1877 a great many papers on physiological albuminuria have been published. MacLean found albuminuria in 5.62 per cent of healthy young soldiers and Diehl and McKinlay in 5.32 per cent of 20,000 male students at the University of Minnesota. Theobald found a trace or more of albumin in the urine of 34 per cent of 110 college girls in one or more samples of urine during the day but only 10 per cent showed albumin in the specimen passed immediately after rising from bed. He also found albuminuria in 16 per cent of girls thirteen to fourteen years of age and in 8.2 per cent of women over twenty-five years of age. He stated that contrary to the general opinion, contamination with vaginal secretion never causes more than a faint trace of albumin.

The consensus is that about 5 per cent of young people show albuminuria but the amount of albumin is nearly always small and it disappears before adult life.

It is well established that in some individuals a slight albuminuria develops after strenuous exercise. Emotional stress may cause proteinuria (Ahronheim).

Influence of Posture. Posture is a very important factor in benign albuminuria. It was first observed that many persons with albuminuria show albumin in samples of urine passed during the day when they are up and about but none in the urine secreted while they are resting in bed. This observation gave rise to the term "orthostatic albuminuria" but it was later discovered that in most of these cases albumin is secreted in the lordotic but not in the kyphotic position. Jehle suggested the test for "lordotic" albuminuria that is now widely used. Specimens of urine secreted while the patient is in a lordotic posture are compared with those secreted in bed or when in a kyphotic posture. If albumin is found in the former but not in the latter specimen the diagnosis of lordotic albuminuria is established. It is believed that lordotic albuminuria is caused by passive congestion of the kidneys due to compression of the renal veins in the lordotic posture. Sonne examined 6 cases by ureteral catheterization in the lordotic position and found albumin only in the urine from the left kidney.

Posture and exercise probably account for the great majority of the benign albuminurias. It is important to bear in mind that benign albuminuria has an excellent prognosis and usually disappears in adult life and it is therefore very important for the clinician to distinguish it from true nephritis. Many young men are given a diagnosis of Bright's disease and denied life insurance because of benign albuminuria. Life insurance companies have a strange unfounded fear of albumin in the urine; they refuse to recognize benign albuminuria.

To distinguish nephritic albuminuria from the benign forms one

should instruct the patient to empty the bladder before retiring and then to collect separately the specimen passed immediately after rising from bed and several specimens passed throughout the day. Frequently albumin first appears in an afternoon specimen. If there is no albumin in the first morning specimen the patient does not have nephritis even though there be heavy albuminuria in the afternoon.

Occasionally one finds individuals who have albumin in both day and night samples of urine without any other symptoms or signs of any disease. Most of these cases are forms of benign albuminuria but the patient should be studied carefully and followed a year or more before latent chronic glomerulonephritis is excluded.

Albuminuria from Injury of the Brain.—Puncture of the brain just caudal to the sugar center is known to cause transitory albuminuria. After spontaneous subarachnoid hemorrhage there is [illegible]

present in fairly large quantities. The finding of albuminuria in a comatose patient may lead to the erroneous diagnosis of nephritis. In one patient at the University Hospital a subarachnoid hemorrhage was followed not only by albuminuria but by a rise of the blood urea nitrogen to 150 mg per cent. Although a diagnosis of nephritis was considered complete recovery took place within a few weeks. Similarly a patient admitted in coma to the emergency ward was thought at first to be suffering from diabetes because of sugar in the urine but it was later learned that he had carbon monoxide poisoning. It is not unusual to find transitory albuminuria immediately after an apoplectic stroke or a fracture of the skull. No satisfactory explanation has been suggested for albuminuria resulting from injury to the brain.

Albuminuria in Renal Disease.—In the benign albuminurias the injury to the glomerular capillaries is so slight that it can seldom be [illegible]

renal insufficiency. *In fact the greatest quantities of protein are excreted in lipoid nephrosis in which there may be no other measurable impairment of renal function while in contracted kidneys with marked nitrogen retention only a trace of protein may be found in the urine.* The escape of protein into the urine is due to injury and increased permeability of the glomerular capillaries; consequently *more protein passes through when the capillaries are patent* (lipoid nephrosis) than when they are obstructed and closed (chronic glomerulonephritis). When the nephrons are greatly reduced in number as in contracted kidneys the opportunity for the escape of protein is correspondingly diminished. It is clear that protein can

escape only from functioning capillaries, the same ones which transmit water, urea and other solutes.

We can see alterations in the capillary walls such as thickening of the basement membrane and increase of endothelial cells, and we infer that these lesions cause an increase of the size of the pores in the basement membranes allowing the protein molecules to escape. Visible ruptures of the capillaries allow erythrocytes to escape.

In hydronephrosis with renal insufficiency there is little or no protein in the urine since there is no primary glomerular injury. In primary hypertension albuminuria, when present, is commonly due to passive congestion from cardiac failure, but it may be due to anemia of the glomeruli from narrowing of the arterioles or to inflammatory glomerular lesions. Passive congestion from cardiac failure is a frequent cause of albuminuria.

In acute glomerulonephritis the amount of protein in the urine at the onset of the disease does not determine the prognosis; there are about as many recoveries from severe as from moderate initial albuminuria. However, the nephritis is still active as long as any albumin is present, and in the acute exacerbations of a chronic nephritis albumin becomes much more abundant.

In estimating the amount of protein in the urine it is common practice to designate the amount of precipitate as + to ++++, but it is realized that this is only a rough estimation. One should determine the amount of protein in twenty four hour samples of urine before giving an opinion as to how much protein is being lost from the blood.

Hematuria.—Gross hematuria refers to conditions in which there is sufficient blood in the urine to give it a reddish color; microscopic hematuria denotes an increased number of erythrocytes in the urinary sediment. The urine of normal persons contains a few erythrocytes, as many as 500,000 may be found in twenty four hour specimens (Addis). Naturally the number of red cells in a microscopic field will depend upon how well the specimen is centrifugalized and how much the centrifugate is diluted in collecting the drop for examination. We should therefore be very cautious in stating the amount of blood present unless an Addis count has been made. However, it is hardly worth while to count the erythrocytes since only marked increases in their number are of any diagnostic significance.

Blood in the urine may come from ulcerating lesions in the urethra, bladder, ureters or renal pelves, or from the glomeruli. We are concerned here only with the renal pelvis and parenchyma. Bleeding from the renal pelvis may be due to tuberculosis, calculi, tumors or ulcerative pyelitis. So-called essential hematuria is due either to hemorrhagic pyelitis or to small glomerular abscesses (see page 118).

Hemorrhage from the renal parenchyma is always glomerular in

origin the erythrocytes escaping from ruptured glomerular capillaries The conditions that favor rupture are overdistention and injury of the capillary walls In severe chronic passive congestion the capillaries are weakened by overdistention and decreased oxygenation of the blood with the result that many of them rupture and *allow erythrocytes to escape into the urine* In acute glomerulonephritis and in acute exacerbations of the chronic form there is sometimes so much glomerular bleeding that the urine has a reddish color and microscopic examination of the urine in these forms of nephritis shows a definite increase of erythrocytes *in nearly all instances* For this reason some writers call glomerulonephritis hemorrhagic nephritis but as will be explained later hematuria is by no means pathognomonic of glomerulonephritis

In glomerulonephritis bleeding takes place from open capillaries those closed by endothelial proliferation do not bleed Therefore the bleeding in itself is not serious since it occurs in capillaries that are not permanently damaged In fact the form of glomerular disease with most intense bleeding (benign hemorrhagic nephritis page 164) has the best prognosis In the terminal stages of chronic glomerulonephritis when nearly all of the capillaries are closed there are few erythrocytes in the urine

In embolic glomerulonephritis the thrombosed capillaries rupture and allow erythrocytes to escape Large numbers of red cells may be found in the urine in this disease Acute forms of primary hypertension often show hematuria because of thrombosis of arterioles or focal glomerulitis Glomerular bleeding may also occur in severe *bacteriemias and purpuras*

From the above account it is clear that red cells in the urine coming from the renal parenchyma are not sufficient to establish a diagnosis of glomerulonephritis

When the glomerular capillaries bleed the red cells pass through the tubules where they are visible in large numbers Rarely they become impacted and block the tubule Sometimes the site of rupture of a capillary may be seen

Hemoglobinuria —When the circulating erythrocytes are hemolyzed in large numbers hemoglobinemia develops and when it is sufficiently intense hemoglobin escapes into the urine The threshold for hemoglobin is apparently fairly high considerable quantities must be injected intravenously before hemoglobinuria develops After injections Ribbert found hemoglobin in the capsular spaces and concluded it was excreted through the glomeruli During hemoglobinemia the tubules become filled with granules of blood pigment which are interpreted as evidence of tubular resorption Whipple and his co-workers found the threshold for *hemoglobin* higher on the first than on subsequent injections which they attributed to stuffing of the tubule cells with blood pigment They

believe glomerular excretion and tubular resorption to be only explanation of their results

After transfusion with incompatible blood hemoglobinemia and hemoglobinuria occur regularly The cells of the donor are hemolyzed by the plasma of the recipient If the urine be alkaline the hemoglobin remains in solution and is excreted in the urine However if the urine be acid the hemoglobin precipitates and fills the tubules with masses of pigment which obstruct the flow of urine and may cause uremia The uremia from transfusion is often due to degenerative tubular lesions (see page 276) Hemoglobinuria occurs also in blackwater fever and from chemical poisons such as potassium chlorate and may be associated with uremia The primary cause is extensive intravascular hemolysis

Hemoglobinuria in the Newborn Winckel in 1879 described an epidemic among newborn infants which he described as afebrile cyanotic icterus with hemoglobinuria The disease is usually fatal within a few days Cyanosis is very marked Fever is not a prominent feature Methemoglobin gives the blood a chocolate color and the urine is brown to black There is increased fragility of the erythrocytes and in smears one finds many nucleated red cells The cause of the disease is unknown

Paroxysmal Hemoglobinuria This disease is characterized by recurring paroxysms of hemoglobinuria following exposure to cold Preceding the hemoglobinuria there is a chill fever pain and other general symptoms The attacks may be induced artificially by exposure to cold Donath and Landsteiner have demonstrated the presence in the blood of a hemolysin which combines with erythrocytes when the blood is cool and hemolyzes them when it is rewarmed The Donath Landsteiner test consists in drawing the patient's blood into a test tube allowing it to cool and then warming it to body temperature Rapid hemolysis occurs on warming when the test is positive The hemolysin is in the serum the erythrocytes of another person may be substituted

Paroxysmal Nocturnal Hemoglobinuria This is a chronic hemolytic anemia with nocturnal hemoglobinuria There is intravascular hemolysis resulting in hemoglobinemia and hemoglobinuria when an excessive amount of hemoglobin is liberated Death may result from anemia intercurrent infections or widespread thromboses The anemia is of normochromic normocytic type with low hemoglobin and a low red cell count Chilling of the blood is not a factor It is postulated that there is an abnormal sensitivity of the erythrocytes to changes in the pH within the normal range The increased acidity of the blood during sleep is believed to cause the hemolysis

Myoglobinuria Myoglobin may be found in the urine after severe crushing injuries of muscles (see Crushing Syndrome) or as a result of degeneration of voluntary muscles

Bilirubinuria Bilirubinuria occurs in all forms of obstructive

urine as soon ʾ With an icterus
index of 15 ra In jaundice
granules of id are usually in
terpreted as evidence of resorption In obstructive jaundice associated with renal insufficiency there is very little bilirubin in the urine Bilirubin is apparently excreted through the glomeruli and the quantity in the urine decreases as glomerular filtration is reduced

Excretion of Dyes —*Phenolsulphonephthalein* —It is clearly established that this dye is excreted in part through the glomeruli since Richards has demonstrated its presence in the glomerular urine of the frog Bieter and Hirschfelder noted that after injection of phenol red the glomeruli of the transilluminated frog kidney have a light pink color But it is also clearly established that this dye is readily excreted by the aglomerular kidneys of the toadfishes (Edwards and Condorelli Marshall) Edwards by study of the transilluminated frog kidney found that phenol red is best seen in tubules associated with inactive glomeruli an active glomerulus washes the dye out of the tubule rapidly Marshall maintains that 80 per cent of phenol red is excreted by the tubules He states that only 25 per cent of the dye is filterable the rest being bound to protein Scheminzky found that phenol red is concentrated 125 times Smith states that 94 per cent of phenolsulphonephthalein is excreted by the tubules and estimates the clearance of this substance at 400—over three times that of inulin

The excretion of phenolsulphonephthalein is independent of the diuresis but in the presence of oliguria the test is of no value since a great deal of the dye is retained in the pelves and ureters

The organic iodine compound *diodrast* is excreted almost entirely by the tubules Diodrast is almost completely removed from the blood during one passage through the kidney so that the diodrast clearance is a measure of renal blood flow Indigo carmine is probably excreted in the same way as phenolsulphonephthalein Oliver and Lund found that neutral red is excreted chiefly by the tubules a rearrangement of the mitochondria takes place during secretion Richards agrees that neutral red is excreted in part by the tubules

Excretion of Bacteria —Wyssokowitch in 1886 found that bacteria were not excreted by the kidneys immediately after injection into the blood stream Staphylococci did not appear in the urine until several hours had elapsed and less virulent organisms were absent up to twenty four hours after injection Since that time numerous experimenters have found bacteria in the urine within a few minutes after injection Helmholz in a series of papers in 1925 and 1926 clarified the discussion He pointed out that the technique of obtaining the urine was of great importance Urine

obtained by catheter was contaminated in 50 per cent of tests and a false positive result is obtained if any blood gets into the urine. The abdomen and urinary bladder must be opened by aseptic technique and the urine collected without contamination with blood. With this method it was found that staphylococci do not appear in the urine until after twelve hours and *E. coli* after twenty-four hours. This delayed appearance indicates that the organisms escape through minute lesions in the glomeruli which they induce and that the normal glomerular membranes are impermeable to bacteria. Definite glomerular abscesses may be found within twelve to twenty-four hours after injection. Helmholz found that the presence of staphylococcic lesions did not increase the permeability to *E. coli*.

Renal Insufficiency.—Apart from clinical symptoms, renal insufficiency is indicated by: (*a*) inability to form a concentrated urine, (*b*) retention of metabolites in the blood, urea, creatinine and other metabolites, and (*d*) decreased clearances of certain foreign test substances, (*c*) decreased elimination of indigo carmine, inulin, diodrast, etc., e.g., phenolsulphonephthalein. Tests made by these various procedures usually agree when there is a marked renal insufficiency but some will disclose a moderate degree of renal insufficiency better than others. With few exceptions all of these diagnostic procedures measure the amount of functioning parenchyma that remains and do not indicate whether glomerular or tubular function is primarily at fault. If either glomerulus or tubule be completely destroyed no urine is formed by the nephron and the entire nephron soon undergoes atrophy.

In rare instances in which the damage is not severe enough to stop all urine formation by the nephron it may be determined which segment is at fault. In the early stages of acute glomerulonephritis there is partial obstruction of the glomerular capillaries with decreased glomerular filtration and a concentrated urine (good tubular function), but this stage is of very short duration (Fishberg). In sublimate nephritis glomerular filtration is not affected but the damaged tubules allow most of the glomerular filtrate to diffuse back into the blood.

When the amount of renal parenchyma is reduced to about one-third of normal by surgical removal, all the signs of renal insufficiency develop although all the remaining nephrons are entirely normal. Since there is a large reserve of renal tissue the parenchyma must be reduced to about one-third of normal before renal insufficiency can be demonstrated. The loss of one entire kidney (50 per cent) produces no disturbance. It must be realized that this does not mean that the total number of nephrons must be reduced to one-third before impaired function is demonstrable, since it often happens, especially in glomerulonephritis, that the number of nephrons is still adequate but the individual glomeruli are ob-

structed in varying degree and can function at only a fraction of their normal capacity

(a) *Inability to Form a Concentrated Urine* —This is one of the best evidences of renal insufficiency The normal person usually excretes a urine which varies 10 points or more in specific gravity in

polyuria About the same [illegible]

[illegible] he is awake and the specific

[illegible] int often ranging between

[illegible] of any sample of urine is 1 025 or more after correction for the amount of protein present it is not necessary to do a concentration test but if the specific gravity of individual samples is low it does not follow that the kidney cannot concentrate The concentration test consists in putting the patient on a diet with a minimum amount of fluid for a twenty four hour period and taking the specific gravity of samples of urine a few hours apart If the maximum specific gravity which is commonly found *in the samples at the end of the period is below 1 020 a definite* impairment of renal function is established One must of course be certain that the patient does not take fluid surreptitiously

It has been maintained that this is a test of tubular function since concentration is effected by the tubules but the same phenomenon [illegible]

parenchyma was greatly reduced in amount but was histologically normal yet the patient excreted a very dilute urine When the kidneys are unable to form a concentrated urine we may infer that there is an inadequate *amount* of tubular tissue but we are not justified in diagnosing tubular disease Fishberg points out that as renal insufficiency becomes more severe the maximum attainable specific gravity of the urine decreases but never goes below 1 010—the specific gravity of blood plasma The most severely damaged kidneys that can excrete any urine can concentrate to *1 010*

Why is a diseased kidney unable to form a concentrated urine? The basic anatomical disturbance is usually *a greatly decreased* number of normal nephrons or a partial obstruction of the glomerular filter in most of the nephrons with or without a decrease of their total number rarely a tubular lesion is responsible The number of functioning nephrons may be reduced not only by glomerular lesions and arteriosclerosis but also by *the pressure of cysts (polycystic* kidneys) the destructive effects of interstitial exudates (pyelonephritis) and hydronephrosis The glomerular circulation may be

obstructed by endothelial proliferation in the capillaries from pressure of epithelial crescents or from narrowing of the afferent arterioles. When the glomerular filter is greatly decreased in size as a result of any of these disease processes it is believed that each open glomerular capillary filters at a maximum rate and the glomerular filtrate passes so rapidly through the tubules that there is not time enough for the tubule to resorb the usual amount of water. When the blood urea is high the glomerular urine has a higher osmotic pressure which must delay the reabsorption of water by the tubules.

Hyposthenuria.—Hyposthenuria refers to a urine with specific gravity less than that of the blood plasma which is 1.010. Frogs and fish normally secrete hypotonic urine. In man a hypotonic urine is found in diabetes insipidus (specific gravity 1.003 to 1.005) in which the failure of the tubules to resorb water is attributed to lack of the hormone pitressin. Hyposthenuria may also occur in normal individuals after ingestion of large quantities of fluid. The dilution test consists in having the patient drink about 1200 cc of fluid within half an hour and measuring the volume and specific gravity of samples voided at the end of each hour for several hours. The normal individual responds by excreting all the surplus fluid within four hours and the specific gravity of the urine falls to 1.003 or lower. The individual with renal insufficiency shows no great increase of urine volume in the hour sample and is unable to form a dilute urine, the specific gravity remaining about the same as previously. The mechanism by which the kidney forms urine with a specific gravity below that of the glomerular filtrate is not understood. We may believe that it consists in normal resorption of solutes but decreased resorption of water.

(b) *Retention of Metabolites.*—When the amount of functioning parenchyma has decreased to about one-third of normal the various metabolites normally excreted in the urine begin to increase in the blood. This is due primarily to decrease of the glomerular capillary area through which filtration must occur. The increase in blood metabolites must therefore be attributed to decrease in the total quantity of glomerular filtrate. The urine output may be increased but its specific gravity is subnormal and the twenty-four hour excretion of urea may be diminished. The substances which increase in the blood in renal insufficiency are chiefly urea, uric acid, creatinine and phosphates. It is ordinarily sufficient to determine the level of blood urea. A persistent blood urea nitrogen of 30 mg per cent indicates severe renal insufficiency. Commonly the urea nitrogen does not exceed 100 mg per cent until the final stages of the disease. Inasmuch as the blood urea does not increase greatly until the renal function is well advanced it is necessary to use a more delicate test to demonstrate the early stages of renal disease.

One may find the blood urea nitrogen at a level of 30 to 40 mg per cent for many months or even for years and the question arises

as to how this level is maintained by the diseased kidney and why it does not progressively increase. When the blood urea is high a greater amount of urea is contained in the glomerular filtrate and by this means the kidney may be able to hold the blood urea at a constant but increased level. A further destruction of renal parenchyma would of course cause the blood urea to rise to higher levels.

(c) *Decreased Clearance of Blood Metabolites. Urea* (see page 37). —Van Slyke and his co-workers developed the urea clearance test. The clearance of a substance means the volume of blood which contains the amount of the substance excreted in one minute. In its passage through the kidney the blood loses only about one-half of its urea content. Under normal conditions the amount of urea excreted per minute varies directly with the urea concentration of the blood. The clearance does not measure the amount of urea excreted but the number of cubic centimeters of blood which contains the amount of urea excreted per minute, or the volume of blood completely cleared of urea per minute. The urea clearance is expressed in percentage of normal. A correction must be made for surface area in children and small adults. In normal subjects there may be marked variations in urea clearance from time to time. The maximum clearance is more accurate than the standard clearance. A clearance below 50 per cent of normal means impaired renal function. The urea clearance is usually below 40 per cent of normal before the blood urea is increased. In a nephritic with compensatory polyuria there may be a good urea clearance. Van Slyke and associates found in dogs that the urea clearance was over twice as great on a high as on a low protein diet. They attribute this to variations in renal blood flow induced by the diet and not to differences in the percentage of urea extracted from the blood by the kidneys. A good practical discussion of urea clearance is given by Fishberg.

Creatinine Clearance. The creatinine clearance was developed by Rehberg. It gives about the same information as the urea clearance and is more difficult to do accurately.

(d) *Decreased Elimination of Foreign Test Substances. Phenolsulphonephthalein.*—The phenolsulphonephthalein test introduced by Rowntree and Geraghty in 1912 is a simple procedure and is widely used. The dye is excreted chiefly by the tubules although a fraction of it passes through the glomeruli. An intravenous injection of 1 cc. of a standard solution is given, and the percentage excreted during a two-hour period is determined with a colorimeter. It is best to have the patient drink about 300 cc. of water at the beginning of the test to produce a good flow of urine since with a low diuresis much of the excreted dye may be retained in the pelves and ureters. If the patient has residual urine catheterization is necessary. The two-hour elimination is usually more accurate than the thirty-minute excretion since there is less chance of retention in

the pelvis and ureters * The greater part of the dye is excreted du[illegible] ing the first hour The normal two-hour excretion is 60 to 70 p[illegible] cent An excretion of 30 per cent indicates moderate and below 1[illegible] per cent severe renal insufficiency But any condition which de[illegible] creases renal blood flow causes a decreased excretion of the dye In passive congestion from cardiac failure the output may fall below 30 per cent from otherwise normal kidneys The excretion of phenolsulphonephthalein may fall to zero before the blood urea nitrogen is above 40 mg per cent In chronic renal disease this test gives convincing evidence of renal insufficiency earlier than does the determination of blood urea The urea clearance test is however usually considered more delicate

A patient with severe renal insufficiency may have a daily output of 1500 cc of urine and yet excrete no phenolsulphonephthalein The kidney contains some functioning tubules and one would expect a small amount of dye to be eliminated by a kidney which can excrete appreciable amounts of urea But apparently the tubules do not excrete the dye when they are greatly reduced in number

Indigo carmine is used by urologists in unilateral renal disease to determine the function of the diseased kidney With a catheter in each ureter the time of appearance of the dye from each ureter is noted and the intensity of the color of the urine from the diseased kidney is compared with that from the normal side Often the diseased kidney shows a marked delay in the appearance of the dye and the urine has little or no blue color

Diodrast —This iodine compound is radiopaque and is used for intravenous urography since it outlines the renal pelves and the kidneys In the presence of even a moderate renal insufficiency it is excreted in such small amounts that no shadow of the kidneys or pelves can be obtained Diodrast is most useful in unilateral renal disease in which it may often be shown that one kidney is normal and that the other excretes no diodrast

Diodrast is excreted largely by the tubules White found the diodrast clearance in the dog to be 240 cc per minute per square meter at plasma iodine levels between 1 3 and 13 mg per cent The tubular excretion of diodrast rises linearly with increase of plasma level up to about 13 mg per cent Above 20 mg per cent no further increase occurs indicating that there is a limit to the quantity that the tubules can excrete in a unit of time When the tubules are poisoned with phlorhizin the tubular excretion of diodrast falls to about 60 per cent of normal (White)

Homer Smith found that diodrast is held almost entirely in the plasma and that it is completely excreted from the blood in its first passage through the kidney Smith therefore used the diodrast clearance as the measure of renal blood plasma flow However,

* Chapman and Halsted prefer the fra[illegible] [illegible] test 15 [illegible] 30 mi[illegible] to the two-hour test They [illegible] [illegible] its excret[illegible] [illegible] [illegible] to some extent [illegible] [illegible] [illegible]

White and Heinbecker found that about 11 per cent of the diodrast in the urine comes from blood cells and suggested that the renal blood plasma flow may be obtained by multiplying the diodrast clearance by 1 2

The maximum secretion of diodrast per minute (average about 40 mg) is a measure of the tubular excretor

diodrast clearan

(normal ab

functioning

ischemia ... blood flow to the ... this figure is well below 13 it indicates

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CHAPTER IV

DEVELOPMENTAL ANOMALIES

A RENAL AGENESIS

1 **Bilateral Renal Agenesis** —Complete absence of both kidneys is observed occasionally in laboratories where many autopsies on the newborn are carried out In our series of 59 064 autopsies on the 21 cases of bilateral renal agenesis 1 to 2812 Among 4512 stillborn infants there were 10 cases 1 to 451 Rosenbaum 1931 collected 92 cases from the literature Madisson 1934 reported 4 cases and added 9 others from the literature Amolsch 1937 surveyed 119 cases including 4 of his own Solowav 1939 found twenty cases in 25 000 autopsies Hinman 1935 brought the total reported cases up to 135 Potter 1946 found 20 cases among 5000 autopsies on infants 1 to 250 Potter described a peculiar facies which she considers characteristic of the anomaly

The anomaly is more frequent in males males 51 females 20 (Madisson) Seventeen of our 21 cases were males The infants are often stillborn 10 of our 21 cases and they seldom live over a few hours The length of life of the eleven infants born alive varied from a few minutes to six hours but there is one report of an infant that survived eleven days Two of Madisson's cases were from the same mother at separate pregnancies

Bates, 1933 stated that oligohydramnios was present in every case in which the amniotic fluid was noted and concluded that the amniotic fluid is chiefly fetal urine but there are many reports in which a normal amount of amniotic fluid was present

There is complete absence of both kidneys and usually of both ureters also but portions of the ureters may be present In 8 of our cases the bladder also was completely absent and in 6 others it was very small Some other developmental anomaly is nearly always present especially in the caudal part of the body Thirty-seven of 51 males had absence or malformation of the genital organs especially the testes and 18 of 20 females had anomalies of the sexual organs (Madisson)

Twenty of our 21 cases were premature infants and all but one had some anomaly other than renal agenesis Three had imperforate anus and 1 had spina bifida Occasional cases are reported in which renal agenesis is the only anomaly

2 **Unilateral Renal Agenesis** —Solitary kidney in the broad sense includes all instances in which one kidney is of normal size or enlarged and the other entirely absent or very small We may distinguish three types of solitary kidney in the broad sense (*a*) Complete absence of one kidney and ureter (*b*) complete absence

of one kidney with the presence of part or all of its ureter, and (c) one normal kidney and the other present only as a rudiment incapable of sustaining life if the normal kidney be removed. The first two groups are clearly examples of agenesis, but the third group belongs either with primary hypoplasia or secondary atroph... sion of agenesis the third gro... sible. In collected stat... three groups.

Frequency.—Anders collected 286 cases of solitary kidney. . u feldt found 10 cases in 4500 postmortems. Fortune, 108 cases in 139,346 collected postmortems, 1 to 1290; Campbell, 76 in 122,320 collected postmortems, 1 to 1610. Thompson, 32 in 12,888 post mortems from three hospitals, 1 to 400. The most comprehensive survey is given by Collins, 1932, who collected 572 cases from 337,488 postmortems, 1 to 920.

In our series of 59,064 postmortems there were 96 instances of complete absence of one kidney, an incidence of 1 to 615. The greater frequency of this anomaly in our postmortems is due to the inclusion of a relatively large proportion of stillborn and very young infants. In 4512 stillbirths there are 21 cases, 1 to 215, while in the rest of the group the ratio is 1 to 740. In the stillborn group there are many with severe malformations, and these have a higher in cidence of renal anomalies.

Age.—Solitary kidney may be found at any age, which is to be expected since one kidney is amply sufficient to maintain life even though not hypertrophied. In his analysis of ... found the following age dist... 38, two to twenty-one ye... 63. Twenty-one of our 9... were less than one week ol... through the various decades as follows: ...s were distributed to ten years 6, ten to twenty years 2, one week to 1 year 5, one thirty to forty years 9, forty to fifty years 11, twenty to thirty years 3, sixty to seventy years 10, fifty to sixty years 8, ninety-six years 2, seventy to eighty years 8, eighty to

Sex.—In his summary of the literature Collins found 281 males and 231 females, but this difference is probably not significant since there are more males than females in postmortem records. In our postmortem records, exclusive of stillbirths, there are 34,982 males and 19,570 females. In this group there are 52 males and 23 females with a single kidney. This gives the incidence of unilateral agenesis of 1 to 0.73 in males and 1 to 851 in females.

Position of the Anomaly.—In his extensive survey Collins found the left kidney absent in 54.7 per cent, the right in 40.9 per cent, and side not stated in 4.3 per cent. In our group of 96 cases the left kidney was absent 50 times, the right 43 times, and there were three cases with a pelvic kidney in the midline.

The Weight of the Single Kidney —The single kidney is usually larger than one of a pair of normal kidneys In 11 adults Motzfeldt found an average weight of 256 gm In 44 of our adult cases the weight of the kidney is recorded as follows 120 gm 1 150 to 199

The Ureter of the Absent Kidney —In many reports no mention of the ureter is made and it is therefore difficult to determine how frequently it is absent Fortune in a review of 422 cases found the ureter noted as absent in 54 per cent and present in 10 per cent McNally noted absence of the ureter in 17 of 20 cases and Campbell in 8 of 9 cases In our group of 96 cases the condition of the ureter was noted in 74—it was completely absent in 59 and a remnant or the entire ureter was present in 15 In the 15 instances in which some ureter was present two showed only the meatus in the trigone and no ureter external to the bladder in three cases it was a fibrous cord terminating in a small cyst in the renal fossa in four it was a short segment adjacent to the bladder in two it was partly patent and partly occluded in one it was patent throughout and three ureters were merely noted as present

According to published reports the ureter varies from a mere dimple in the trigone to a full length structure terminating in the renal pelvis It is usually impermeable in the greater part of its course and it is often merely a fibrous cord Some writers do not accept cases in which any part of the ureter is present as examples of pure renal agenesis But this interpretation seems extreme since the ureter is not the kidney and it is probable that the ureteral bud *does not reach the metanephric blastema in the vast majority of* these cases In instances in which a kidney remnant is present containing glomeruli we are obviously not dealing with complete agenesis but even these cases probably represent defective development and not atrophy of a previously formed kidney

Structure of the Kidney Remnant —A few authors have described the microscopic structure of the rudiment occasionally found in the renal fossa to which a ureter is connected Fortune and MacKenzie both mention tubules and glomeruli in these structures Tubules might be derived from the ureteral bud but the presence of glo-

developed only to a slight extent They are to be interpreted as *extreme hypoplasia but not as complete renal agenesis*

Associated Anomalies —Other congenital anomalies are found in many cases of unilateral renal agenesis the great majority of which in adults are defects in the genital organs According to Fortune about two-thirds of the females show malformations of the genital tract usually the uterus These anomalies are due to incomplete fusion or defective development of the mullerian ducts (bicornate uterus unicornate uterus double uterus atresia of vagina etc) In males there is often unilateral absence of the ductus deferens ejaculatory duct seminal vesicle and sometimes a part of the epididymis—these structures are derivatives of the caudal portion of the mesonephros

In our experience associated anomalies are uncommon except in infants In 51 of 55 cases over eight years of age there was no *other abnormality 1 had uterus unicornis 1 had asymmetry of* the legs 1 showed absence of the left testis and epididymis as well as the left kidney and 1 showed absence of the right adrenal uterus and vagina However in 16 of the 26 infants there was some other gross anomaly such as spina bifida meningocele encephalocele,

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side grows caudally and establishes an opening into the cloaca The ureteral bud from the wolffian duct gives rise to the ureter, the renal pelvis and the collecting tubules the other segments of the renal tubule and the glomeruli arise from the metanephric blastema

Boyden has offered a satisfactory explanation of renal agenesis

reached the cloaca and no ureter had developed on the left side The left renal blastema had appeared but had not developed into tubules The arrested development of the mesonephros is therefore the factor underlying renal agenesis Boyden points out that ureteral and renal agenesis may be produced experimentally in chick embryos by

to lack of the metanephric blastema Since the ureter is ... about 80 per cent of cases of renal agenesis it may be inferred that in these cases no ureteral bud developed from the wolffian duct When only a part of the ureter is present it is probable that the ureter fails to reach the renal blastema The frequent absence of the ductus deferens and seminal vesicle suggests a failure of development or a

retrogression of the caudal portion of the mesonephros from which these structures are derived. The associated malformations such as meningocele indicate more widespread disturbance in the embryonic body.

Disease of the Solitary Kidney. There is a widespread opinion in the literature that a solitary kidney is more prone to disease than a normal kidney. Collins found that disease of the single kidney was recorded in 18.9 per cent of cases from the literature, but this incidence is probably too high since many observers diagnose simple *arteriosclerotic changes as nephritis.* *Among the infants in our* series there were 2 instances of hydronephrosis, 2 cases of small polycystic kidney and 1 hypoplastic pelvic kidney with only two pyramids. Among the adults there were two cases of congenital hydronephrosis, a male aged 34 years and a female aged twenty-nine years. There were two other cases of hydronephrosis of undetermined origin. A male aged 71 years had a pelvic kidney with hydronephrosis due to a calculus. There were 4 cases of chronic glomerulonephritis in persons aged eight, thirteen, nineteen and thirty-four years respectively. The patient aged nineteen years had a pelvic kidney. There were 4 examples of ureteral duplication and there were 3 pelvic kidneys mentioned above. Only the 3 patients [illegible] Waller reported 2 [illegible] ckenzie recognized [illegible] idney. Apparently there is occasionally some anomaly of the ureter which leads to hydronephrosis and infection, but the single kidney is not a great hazard to life.

Unilateral kidney may be recognized by the urologist from cystoscopic examination or by the pyelogram. When a double uterus is found there is a possibility of a single kidney. Reusch and Unseld each reported two clinical observations of double uterus and single kidney. Tscherne found a wolffian duct cyst in the broad ligament *and behind the uterus in a woman with a double uterus and a single* kidney. Hyman removed a calculus from the ureter of a single kidney and inserted an artificial ureter. The patient had a bicornate uterus.

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B RENAL HYPOPLASIA

1 Unilateral [illegible]
term dwarfed
reference to etio
of defective development of its anlage (true hypoplasia) or its smallness may be due to secondary atrophy from urinary obstruction arteriosclerosis or interstitial nephritis There is abundant evidence that complete urinary obstruction may lead to marked atrophy of a kidney after the lapse of many years but we have not included among the dwarfed kidneys any case which was obviously

thirds to three-fourths of the renal tissue is removed We have adopted 60 gm as the minimum amount of renal tissue capable of sustaining life in an adult although there is no direct clinical evidence that this is an accurate estimation The great majority of dwarfed kidneys have no functioning parenchyma so that even their small size exaggerates their physiological importance Only the cases in Group 1 had normal parenchyma

On the basis of their structure and other evidence the dwarfed kidneys in our collection have been subdivided into several groups

GROUP I True Hypoplasia Without Secondary Atrophy or Cysts (Table 1) —In the 18 cases of this group the parenchyma of the small kidney was considered normal by the pathologist on macroscopic examination but the diagnosis of hypoplasia was based upon the reduced number of pyramids Nos 1 3 and 5 were preserved and have been reexamined by me The renal parenchyma in all three cases showed a normal microscopic structure

The small kidneys of this group differ therefore quantitatively

but not qualitatively from the normal They show a reduced number of reniculi, 3 to 5 instead of the normal number of 12 to 14 Gruber has collected several such cases from the literature Pelvic

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the normal kidney indicates that the anomaly has been present for many years

TABLE 1 —GROUP 1 TRUE HYPOPLASIA WITHOUT SECONDARY ATROPHY OR CYSTS

Serial no	Autopsy no.	Age	Sex	Weight of right kidney gm	Weight of left kidney gm	Number of pyramids	Weight of least gm	Blood pressure	Comment
1	14 159	25	M	300	30	5	340		
2	24 718	26	M	large	30	?	326		
3	26 338	5 mo	M	30	35	3	norm		
4	30 1184	46	M	240	60	?	300		
5	34 308	64	M	100	30	3	[illegible]		Ectopic
6	36 1625	55	M	213	45	?	355	140/68	
7	37 781	65	M	60	50	?	400	116/92	Atrophic segment in center
8	39 742	55	F	[illegible]	75	4	[illegible]	[illegible]	
9	41 084	30	F	45	160	4	600	200 140	Malignant hypertension
10	41 2724	65	F	[illegible]	10	few	[illegible]	135 70	Uremia abscesses
11	42 757	1 day	F	2	8	?			
12	44 447	21	F	50	110	4	210		
13	44 880	31	F	15	490	4	360	134 92	
14	44 2208	0	F	1	13	?			
15	45 479	76	F	110	25	6	350		
16	45 1091	24	F	210	[illegible]	2	[illegible]		
17	47 2313	3 mo	M	3	13	?	30		
18	47 2341	69	F	200	[illegible]	6	600	200 100	

Clinically this form of hypoplasia is readily recognizable by

resulted from uremia from a few days to nine years after removal of the larger kidney In 2 of these the ureter of the larger kidney was blocked by a calculus and the small kidney was unable to sustain life after the nephrectomy

GROUP 2 **True Hypoplasia With Cysts** (Table 2) —Six of the 16 patients were infants and in 4 of the infants the small kidney was represented by a small cystic mass without macroscopic evi-

ulus with tubules was found microscopically In No 26 the small kidney showed a fair amount of normal parenchyma between the cysts and atrophic areas The normal kidney showed a marked hypertrophy as in Group 1 Nine of the small kidneys were available for microscopic study

The cases of Group 2 may be interpreted as unilateral cystic disease

GROUP 3 **Atrophy of Undetermined Etiology** (Table 3) —In the 66 cases of this group the atrophy was usually so extreme that the lobules could not be identified In 5 instances small areas of normal cortex were recognized but in the other 61 cases the cortex was a thin layer of atrophic tubules the glomeruli being either hyaline or com

TABLE – GROUP 2 TRUE HYPOPLASIA WITH CYSTS

Serial no	Autopsy no	Age years	Sex	Weight of right kidney gm	Weight of left kidney gm	Normal parenchyma	Cysts	Atrophy	Weight of heart gm	Blood pressure	Comment
19	14 17	51	F	20	40	2	1	1	Norm		
20	24 4??	67	M	10	180	0	4	0	260		
21	24 656	30	F	Norm	Small cyst	0	4	0	2?		
2	?6-784	SB	M	Large	Small	0	4	0	Norm		
23	29- 96	21	M	20	? 4	1	0	3	?		
24	32 ?1	4 5 mo	F	Very small	3 5	1	1	2	Large		
?	3? 549	60	M	2?0	9?	0	4	0	380	160 94	
6	33 804	2 mo	M	25	8	2	0	2	3		
27	33 10?3	3 da	M	15	??	1	2	1	17		
8	33 1655	?0	F	?0	Cystic mass ?30	3	1	0	2?0		
?1	34 212	34 hr	M	2	Fibrous mass 1 7	1	4	0	6		
30	35 1887	6?	F	4?	43	1	4	0	650	220 136	Few nephrons
31	37 901	??	M	1 0		?	1	3	500	125 86	
3	38 1640	12 da	M	Twice Norm	Very small	1	3	0	23		Right 50% cysts Left—a few cysts
33	40 117	68	M	40	cystic ?0	0	3	4	3?5	1 0 100	Ectopic
34	40 944	0	F	??5	?5	0	4	4	3??	1 ? 1 ?	One normal re- n culus

pletely absent The cortex frequently showed the thyroid appearance shown in Figure 10 Many of these kidneys were probably hypoplastic originally but some other process such as atherosclerosis or pyelonephritis must have been superimposed In a majority the large sclerotic arteries suggest that the kidney had originally been larger When the normal kidney weighs over 175 gm it is highly probable that the lesion originated early in life On the other hand a normal kidney weighing 160 gm or less suggests a secondary atrophy late in life

In 38 cases the normal kidney weighed 200 gm or more which indicates strongly that the anomaly was congenital or that the small

TABLE 3 — GROUP 3 ATROPHY OF UNDETERMINED ETIOLOGY

Serial no	Autopsy no	Age	Sex	Weight of right kidney gm	Weight of left kidney gm	Normal parenchyma	Atrophy	Weight of heart gm	Blood pressure
35	15-35	20	M	5?9	3 x 2 x 0 5 cm	0	4	4.	
36	15-44	39	M	50	300	0	4	Norm	
37	20 210	13	F	1?0	11 5	0	4	2?0	
38	25-607	40	M	20	315	0	4	3 0	
39	26 24	36	M	2?5	3 x 5 x 1 cm	0	4	3?5	
40	27-316	27	F	390	Very small	0	4	?	
41	27 86?	56	F	385	10	0	4	2??	
42	29-1191	42	F	?0	190	0	4	400	19?/90
43	29-1446	29	F	0	10	0	4	430	114/?4
44	29-140	12	F	18	110	1	3	230	194/124
45	29 243	68	M	Hypernephroma	38	0	4	510	
46	29-675	74	M	270	60	0	4	?	145/?5
47	29 1089	46	M	Remnant	00	0	4	310	
48	30 9?6	77	M	30	2?0	0	4	360	200/105
49	30-1491	70	M	?00	30	0	4	510	132/00
50	31 992	55	M	5	300	0	4	410	
51	31 1105	43	M	280	3 cm	0	4	383	
52	21 1175	SB	M	5	30	?	?	15	
53	32-401	78	M	Normal	30	0	4	310	10?/?8
54	32 1202	67	M	Very small	360	0	4	400	
55	32 1983	87	F	150	40	0	4	3 0	104/56
56	34 1118	33	F	200	30	?	?	?0	156/82
57	34 1301	65	F	16	209	0	4	440	180/110
58	34 1808	60	M	20	150	0	4	530	208/130
59	35 1039	30	F	5	90	0	4	?	
60	35 1401	42	M	550	25	0	4	8 5	
61	35 1322	2?	F	170	25	0	4	2?0	
62	36 1090	36	F	240	20	0	4	400	14?/90
63	36-1593	SB	M	22	5	?	?	?	
64	37 154	55	M	?30	65	0	4	400	1?4/120
65	37 236	4?	F	?0	235	0	4	550	
66	37-371	33	M	190	30	0	4	?00	256/160
67	37 1507	68	F	18	233	0	4	440	190/110
68	37 1800	57	F	145	35	1	3	590	1?0/110
69	37 1956	77	F	35	145	0	4	45?	140/90
70	38 1283	65	F	150	2?	0	4	?	
71	37 215?	13	F	15	?0	1	3	190	210/150
72	38-400	50	M	425	25	0	4	?25	
73	38 17?0	66	M	Very small	260 (pyelonephr.)	0	4	300	112/90
74	38 2360	?4	M	25	200 (arteriolosel.)	0	4	685	
75	39 311	8?	M	50	185	?	?	500	110/?0
76	39 ?93	?4	M	190	10	0	4	?	225/132
77	40-5??	?0	M	15	2?5	0	4	585	1?8/?0
78	4? 91?	?	M	460	1 5	0	4	6?0	11?/?6
79	41 ??	?	M	45	1??	0	3	300	180/1?0
80	4 ??	55	M	150	15	0	4	4??	
81	4 1311	4?	M	10	?0	(	4	?3	1 gl
82	4 1?01	69	F	14?	5?	0	4	603	?0/160
83	41 ??	50	M	4?0	15	0	4	640	
84	41 1 31	5	M	1??	10	(	4	21	130/1?0
85	41 ?1?	5?	F	??	1	1	3	4 0	1?0/?0
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TABLE 3—GROUP 3 ATROPHY OF UNDETERMINED ETIOLOGY—Continued

Serial no	Autopsy no	Age	Sex	Weight of right kidney gm	Weight of left kidney gm	Normal parenchyma Atrophy	Weight of heart gm	Blood pressure
86	43 2329	56	F	00	1 5	0 4	4?7	115 65
87	44 15?	59	F	20	300	0 4	265	—
88	44 2091	7?	M	118	46	0 3	309	180 80
89	44 21??	69	M	340	5 x 2 cm	0 4	5?0	118 75
90	45–210	?	F	160	50	1 3	2?0	—
91	46–14?	75	F	50	250	1 3	69?	180 100
92	46–416	57	F	400	13	0 4	390	140 60
93	46–216	54	M	10	190	0 4	235	100 70
94	46–2?73	53	M	10	280	0 4	695	—
95	46–26??	?5	M	35	200	0 3	290	130 84
96	47 1630	?0	F	?	250	0 4	355	—
97	47 2639	60	M	20	425	0 4	400	—
98	48 233	?4	F	10	185	0 4	250	90 50
99	48–658	?1	F	18	75	0 4	350	180 84
100	48 2764	63	F	390	2 x 1 cm	0 4	485	100 110

kidney became atrophic before middle life It is known that the removal of one kidney in middle life or later does not result in hypertrophy of the remaining kidney but it is not known at what age hypertrophy ceases to occur We have one record of accidental ligature of the right ureter in a woman twenty four years old and at postmortem thirty years later the left kidney weighed 300 gm Therefore it cannot be assumed that a dwarfed kidney weighed 300 gm with a mate weighing 250 gm or more is a congenital anomaly

It might be anticipated that many dwarfed kidneys are due to unilateral interstitial nephritis (pyelonephritis) in early life, but a definite lymphocytic infiltration was found in only 2 instances Nos 44 and 73 We cannot however rule out pyelonephritis because of the absence of an interstitial exudate since it is probable that lymphocytes would disappear after many years

A notable feature of these dwarfed kidneys is the complete absence of normal parenchyma in the vast majority In 5 of the 66 cases there were very small areas of functioning parenchyma but in all the others the cortices were extremely thin and tubular atrophy was pronounced The usual appearance of the cortex is shown in Figure 10 There are closely packed tubules lined by low dark epithelium and filled with casts The resemblance to thyroid tissue is so striking that it is usually referred to as the "thyroid structure" Commonly no glomeruli are present but there may be many hyaline glomeruli and occasionally glomeruli are found which still retain a normal structure Small segments of tubules persist after all traces of the glomeruli are gone

It is clear from the histological study of these dwarfed kidneys that many of them have undergone secondary atrophy, but it has not

been determined whether they were originally hypoplastic or of normal size. As to the pathogenesis of the "thyroid" structure all stages of the process may be seen in the atrophic areas of arteriosclerotic kidneys. Following the narrowing of the artery the tubules first shrink so that the different segments become indistinguishable. The glomeruli gradually become hyaline and in time disappear largely or completely. The atrophic areas in pyelonephritis undergo a similar gradual transition to the "thyroid" structure. We may therefore believe that the dwarfed kidneys of Group 3 are the result of either arteriosclerosis of the renal vessels or pyelonephritis. The thickened arteries may be interpreted as primary atherosclerosis or disuse atrophy.

In Nos 44 and 73 there is some evidence that pyelonephritis was the cause of the atrophy, but if this lesion was a factor in the other cases all traces of it have disappeared. There is, however, strong evidence that arteriosclerosis is responsible for many cases of atrophy. In Nos 43, 45 and 60 death was due to uremia, and severe arterial and arteriolar lesions were found in both the large and the small kidneys, but more pronounced in the latter. In several of the cases with hypertension thick arteries and arterioles were found in the large kidneys. The evidence is not conclusive but favors the view that many of the dwarfed kidneys of this group are caused by arterial disease.

It will be noted that hypertension (systolic 150 mm Hg or higher) was present in 21 of the 37 cases in which the blood pressure was recorded, and the weight of the heart suggests hypertension in 4 of the cases with low blood pressure, as well as in 7 others in which the blood pressure was not taken. In Nos 77, 78, 80 and 94 the cardiac hypertrophy was due to old valve defects. It may be argued that the hypertension was due to the small kidney, but the evidence is much stronger in support of the view that these are cases of primary hypertension with secondary atrophy of one kidney. In the Goldblatt experiment hypertension produced by unilateral renal ischemia disappears after the ischemic kidney has undergone complete atrophy, since there is no longer any renal parenchyma left to form renin. This topic is discussed more fully on page 383.

GROUP 4. **Secondary Atrophy Due to Arteriosclerosis** (Table 4). In this group of 25 cases there was strong evidence that arteriosclerosis was the cause of the atrophy. A majority of the patients had hypertension and the vascular changes were present in a lesser degree in the larger kidney. The atrophy was not so pronounced as in Group 3; there was usually some normal parenchyma present and the different stages of arteriosclerotic atrophy were readily recognized. A study of the kidneys in this group lends support to the interpretation offered for Group 3, viz., that they represent mainly arteriosclerotic atrophy. It is suggested that the atrophy in Group 4 occurred relatively late in life since there is not much

hypertrophy of the larger kidney. No. 123 is a case of hypertension due to stenosis of the right renal artery resulting from thrombosis. There was no evidence of primary hypertension.

GROUP 5. The 20 cases of this group showed very small kidneys with dilated pelves and thin cortices, and no ureteral obstruction. There is abundant evidence in our records that chronic ureteral obstruction frequently leads to atrophy of the kidney, but every case of atrophy clearly due to ureteral obstruction is classified with the hydronephroses.

TABLE 4. GROUP 4. SECONDARY ATROPHY DUE TO ARTERIOSCLEROSIS

Serial no	Autopsy no	Age	Sex	Weight of right kidney gm	Weight of left kidney gm	Normal parenchyma	Atrophy	Weight of heart gm	Blood pressure
101	15 293	66	F	150	18	0	4	?	150/?
102	18 222	60	M	Norm	50	1	3	300	
103	29 1455	81	M	160	50	1	3	460	200/170
104	31 1737	64	M	193	44	1	3	520	230/140
105	33 1302	56	M	40	210	2	2	300	158/90
106	34 334	72	M	50	170	2	2	530	162/90
107	34 992	58	F	106	50	2	2	312	150/92
108	32-837	82	M	50	110	1	3	290	98/60
109	35 1675	81	F	150	35	?	?	570	178/80
110	35 2090	84	M	32	127	0	4	490	160/90
111	35-2102	55	F	59	183	3	1	450	146/90
112	36-66	71	F	30	110	1	3	300	
113	36-177	16	M	115	30	1	3	375	172/116
114	36-856	51	F	40	110	*	*	520	236/120
115	36-1912	53	M	55	190	1	3	490	
116	36-1948	88	M	50	125	0	4	260	135/80
117	36 2162	75	M	36	120	2	2	290	
118	36 2340	57	F	15	Norm	1	4	225	
119	37 1046	69	M	175	27	1	3	605	220/170
120	37 2067	49	F	200	20	1	3	600	160/140
121	37-465	46	F	128	28	1	4	437	142/90
122	43 1141	53	M	30	210	0	4	600	100/80
123	44 198	13	[illegible]	43	195	1	3	317	200/150
124	46-2713	65	F	70	10	0	4	310	130/60
125	48 139	75	F	45	160	1	3	470	190/100

There are at least nine cases of hypertension in this group. In No. 137 the small kidney was removed 10 months before death. The blood pressure was unaffected by the operation. Both kidneys showed severe athero- and arteriolosclerosis.

Frequency of Dwarfed Kidney.—Sokolow found 50 cases in 50,198 postmortems, 1 to 1000. Our records show 145 cases in 59,064 postmortems, 1 to 407. Sokolow had 29 males and 21 females. Our records show 82 males and 63 females, an incidence of 1 to 437 in males and 1 to 343 in females. The right kidney was dwarfed in 68 and the left in 77 of our 145 cases.

TABLE 5.—GROUP 5. SECONDARY ATROPHY PROBABLY DUE TO HYDRONEPHROSIS

Serial no.	Autopsy no.	Age	Sex	Weight of right kidney, gm	Weight of left kidney, gm	No. normal pyramids	Atrophic	Weight of heart, gm	Blood pressure
126	12 112	60	M	213	43	0	4	300	
127	14 51	50	M	110	Very small	0	4	410	
128	15-390	35	F	Enlarged	3 x 1.5 cm	0	4	Norm	
129	16 213	35	M	3 x 2.5 x 1 cm	231	0	4	333	
130	21-804	74	M	5 cm long	Norm	0	4	707	120/76
131	36 1066	60	M	150	37	*	*	334	145/95
132	36 1106	67	M	185	39	0	4	668	170/112
133	38 353	3 hr	M	8	1	0	4	14	
134	37 844	37	M	25	150	0	4	250	
135	41 030	40	F	100	[illegible]	0	4	275	
136	41 1075	72	F	255	45	0	4	350	150/100
137	41 2042	58	M	80	4 x 2.5 cm	1	3	400	210/142
138	44 11	75	M	40	120	0	4	560	180/100
139	44 28	77	M	220	40	0	4	500	108/60
140	44 156	65	M	180	80	0	4	420	190/100
141	44-649	47	F	220	20	0	4	365	200/110
142	44 1078	44	M	45	250	1	3	725	155/105
143	46 2113	72	F	110	15	0	4	430	110/95
144	47 327	60	M	10	400	0	4	475	120/60
145	48 679	59	F	20	150	0	4	350	162/98

From the clinical standpoint unilateral dwarfed kidney has the same significance as complete absence of one kidney since the small kidney alone is incapable of ma[illegible]
was a si[illegible]
out of [illegible]
unilater[illegible] [illegible] estimate from our autopsy records, as exclusive of clinical renal disease, 1 in every 245 persons has only one kidney capable of sustaining life.

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2. Bilateral Renal Hypoplasia. There are numerous reports in the literature dealing with bilateral renal hypoplasia of extreme degree which are in effect the same as bilateral agenesis and resulted in death shortly after birth, but I have found only 1 case in which the child lived long enough to develop a picture of chronic renal disease.

Greene (1922) described such a case in detail. The child aged three and a half years at death first developed symptoms at the

age of eight months She was markedly dwarfed and rachitic and had evidence of chronic renal insufficiency There was polyuria with a specific gravity ranging from 1 005 to 1 012 (no concentration test) The output of phenolsulphonephthalein in two hours ranged from 4 to 8 per cent The highest non protein nitrogen was 48 mg per cent The blood pressure was 108/70 mm Hg There were no changes in the eyegrounds Death was attributed to uremia with starvation acidosis

The left kidney weighed 10 gm, the right 7 gm Microscopically there were no evidences of atrophy or inflammation The glomeruli were large the tubules so large that they appeared cystic Reconstructions of nephrons were made which showed large dilated tubules but no cysts Greene interprets his case as one with normal but quantitatively insufficient parenchyma The dilated tubules represent attempts at compensatory hypertrophy

The following two cases came under my observation

Case Report 38-1495 —A male child fourteen months of age was admitted to the hospital August 8 1938 because of fever, stiff neck poor appetite and dyspnea The mother had syphilis at the time of her delivery, but serological tests on the infant were all negative Birth was at term and delivery was uneventful The child developed slowly had a right club foot since birth and undescended testes About two weeks before admission he developed fever and loss of appetite Two days before admission he became dyspneic

Upon admission the child was dyspneic and was breathing rapidly He was well nourished but dehydrated The weight was 30 pounds and there was no evidence of dwarfism The temperature was 104° F There were no positive neurological findings except hyperactive biceps and patellar reflexes The urine showed a specific gravity of 1 007 and a heavy precipitate of albumin Hemoglobin 69 per cent Leukocytes 16 700 with 81 per cent polymorphonuclear neutrophils Serological tests for syphilis were negative on the blood and spinal fluid Blood sugar 115 mg per cent Blood calcium 11 5 mg per cent blood phosphorus 23 4 mg per cent Blood urea nitrogen one day before death 176 6 mg per cent The spinal fluid was colorless and showed only occasional lymphocytes

A blood transfusion was given and fluid was administered subcutaneously since little could be given by mouth Only small quantities of urine were passed during his four-day stay in the hospital The temperature fell from 104° to 95° F There were occasional convulsions He became more dyspneic and cyanotic and died on August 12 1938

At autopsy right club foot and undescended testes were noted The heart weighed 35 gm The only other important finding was hypoplasia of the kidneys The right kidney weighed 14 gm and the left 4 gm The number of reniculi was unfortunately not noted The parenchyma of both kidneys appeared normal macroscopically

Upon microscopic examination the cortical tissue of both kidneys is normal except for unusually large dilated tubules (Fig 11) In the medulla there is an excess of connective tissue such as is found in polycystic kidneys but there are no cysts The structure is almost identical with that of the kidneys described by Greene It is evident that in this case as well as in Greene's there was insuffi

cient renal parenchyma to maintain life indefinitely. There is no evidence of cystic disease or any destructive lesion, on the contrary there is hypertrophy of the glomeruli and tubules. It is noteworthy that hypertension does not develop in this form of renal disease. It corresponds to the renal insufficiency produced in animals by removing a large part of the renal tissue (see page 49).

structure



Fig. 11. Kidney from a child with uremia due to bilateral renal hypoplasia. Note large tubules and glomeruli as of normal structure. Photomicrograph.

As further evidence of the effect of a simple decrease of renal parenchyma the following case is cited.

of life 130/70 The blood urea nitrogen was 57 5 mg twenty five days and 102 mg five days before death The concentration-dilution test twenty five days before death showed a range in specific gravity from 1 011 to 1 014

REFERENCE

GREENE C H Am J Dis Child 24 1 1922 (Bilateral hypoplasia)

C ECTOPIA OF THE KIDNEYS (Table 6)

According to Pohlman the ureteral buds from the Wolffian ducts are first seen in the 5 mm human embryo and at 7 mm the renal blastemas lie at the level of the second sacral vertebra In the 10 mm embryo the upper border of the kidneys is at the brim of the pelvis The ascent of the kidneys continues throughout fetal life and at birth they have not yet reached the adult position since in the newborn the lower poles are always in the iliac fossa

F Muller has called attention to the wide variation in the position of the kidneys in adults The position varies with the form of the kidney long narrow organs extend more caudally than the shorter broader types that are usually seen The lower pole of the right kidney frequently lies below the iliac crest especially in the female Less frequently the lower pole of the left kidney is below the iliac crest

The vast majority of ectopic kidneys are displaced caudally on the same side of the body but a few lie in the median line or on the opposite side (crossed ectopia) In crossed ectopia the two kidneys are usually fused but occasionally they are separate In caudal displacement the ectopic kidney lies in the iliac fossa, on the brim of the pelvis or in the pelvic cavity Since the normal kidney frequently extends below the iliac crest, especially on the right only those that lie mainly or entirely below the iliac crest should be considered in an abnormal position The cases that come to clinical attention are chiefly those in which the kidney is in the bony pelvis on the sacral promontory or overhanging the brim of the pelvis The pelvic kidney lies on the posterior pelvic wall often in a median position in the hollow of the sacrum It may displace the pelvic organs laterally or anteriorly An unusual situation was reported by Dorland who found the ectopic kidney under the peritoneum in the left anterior abdominal wall Dorland found 2 similar cases previously reported

Guizetti and Pariset 1911 found 18 ectopic kidneys in 20 000 postmortems Motzfeldt 1914 5 in 4500 postmortems Bugbee 1919 6 in 10 000 urological examinations Campbell 1930 27 in 13 000 postmortems The total of these reports gives 50 cases in 37 500 postmortems or 1 750 Thomas and Barton collected from the literature 106 ectopic kidneys in 87 115 postmortems an incidence of 1 822 In our 59 064 postmortems there were 58 ectopic kidneys 1 1018 The anomaly is more frequent in urologic

TABLE 8.—ECTOPIA OF THE KIDNEYS

Serial no.	Autopsy no.	Age	Sex	Side	Weight, gm.	Location	Disease of ectopic kidney	Weight of heart, gm.	Blood pressure	Comment
1	15 69	6 mo.	F	L		Sacrum				
2	16 204	SB	F	R	Small	Lower lumbar fossa				
3	27 619	44	F	R						
4	23 106	39	M	R	70	Iliac fossa	Hydronephrosis	30		Spina bifida, deformed kidney
5	23 162	15 mo.	M	L	25	Pelvic brim				
6	24 733	22	F	R	120	Pelvic brim		240	120/58	Rounded kidney
7	26 531	19	M	L		Lower lumbar fossa		590		
8	2 1353	53	M	L		Above promontory		39		Flattened kidney
9	25 1193	3 mo.	M	R	13	Above promontory		175		Pelvis posterior
10	25 1334	49	M	L	13	Pelvic brim		840	10 73	Pelvis posterior
11	29 190	54	M	R	24	Lateral pelvis		702	[illegible] 140	Pelvis posterior
12	29 [illegible]	37	M	L	1.5	Pelvic brim		[illegible]		
13	29 1444	21	M	R	200	Pelvic brim		350		
14	29 1667	69	F	R	170	Pelvic brim		3[illegible]		
15	3[illegible] 1363	43	M	L	170	Pelvic brim				
16	31-43	40	M	R	115	Pelvis		3 3	110 [illegible]	
17	31 1594	8	M	L		Sacral				
18	32 591	3 da.	M	L	100	Iliac fossa		1 [illegible]	[illegible]	Rounded kidney, pelvis posterior
19	33 767	1 da.	M	R		Pelvic brim	Hydronephrosis	39	1.0 [illegible]	
20	32 1343	75	M	R	14	Promontory		36[illegible]	11 [illegible]	
21	34 3[illegible]	64	F	R	3[illegible]	Pelvic brim		363	12 [illegible]	
22	34 1091	75	M	L	2 5	Iliac pelvic brim		24		
23	35 1 92	68	M	L	30	Pelvis	Pyelonephritis	2		Rounded kidney
24	35 217	72	M	L	150	Pelvic brim		5[illegible]	1.[illegible] 90	Men [illegible] left kidney absent
25	36 019	74	F	R	[illegible]	Pelvic brim		29		
26	36 1296	6	M	L		Pelvic brim		3.0	154/56	Left has 4 renculi, right has 9 renculi
27	37 2	78	F	R	115	Pelvic brim		400	24[illegible] 140	
28	37 233	42	M	L	130	Pelvic brim		300		
29	37 1[illegible]0	69	F	R		Iliac fossa	Pyelonephritis	315		
30	37 19 1	84	M	R		Median 3rd lumbar				Bilaterally hydronephrosis and pyelonephritis from cystitis
31	3 2[illegible]	3 mo.	M	R	3	Pelvis		[illegible] 340		
32	24 301	45	M	R	15	Pelvic brim		[illegible]65	2[illegible] 90	Left turns anteriorly
33	35 1166	23	M	L	130	Pelvic brim	Hydroureter	310	120 [illegible]	Left hydronephrosis, bicornuate uterus
34	35 1598	41	F	R	Large	Pelvic brim		103		
35	35 2553	61	F	L	[illegible]	Iliac fossa		4[illegible]		
36	35 [illegible]	51	M	R	16	Promontory				
37	39 11	83	M	L	91	Pelvic brim		320	1[illegible] 130	Left has 2 renculi
38	25 14	58	F	R	1 5	Pelvis		295	2 4 140	
39	6 100	6	F	L	93	Pelvic brim				
40	6 [illegible]	[illegible]	J	L		Sacrum		4 0	12[illegible]	
41	41 1[illegible]	69	M	R	110	Pelvis		3[illegible]0	17[illegible]	
42	41 2 [illegible]	[illegible]	M	R	1 5	Pelvis		4 3	1[illegible] 130	
		9	M	L	85	Sacrum	Pyonephrosis	4[illegible]	130 [illegible]	
			M	L	1 3	Pelvis	None	4.3	186 110	Right is ectopic. Hydroureter
							None	4 [illegible]	1[illegible] [illegible]	
							None	4 3	15 [illegible]	

renal ectopia without fusion and Mayers 1936 collected 20 cases of this type. About 25 cases have been reported (Harris).

Our single case of crossed ectopia without fusion was in a male 69 years of age who died of carcinoma of the anus. The right kidney was in its normal position. The left kidney was on the right side just above the brim of the pelvis and its artery arose from the right common iliac. It exhibited a severe hydronephrosis due to the carcinoma.

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Movable Kidneys.—The kidneys may be displaced caudally from 1 to 5 cm with deep inspiration. However, Muller has pointed out that the extreme mobility often demonstrable at postmortem does not exist in life but is due to postmortem relaxation of the tissues. The kidney is held in position by its pedicle, its capsule, its peritoneal attachments and the intra abdominal pressure. When these supports are relaxed the kid... wards when the body is in the ...

Kidneys ... only 20 ... females 20 ... toms of 4 ... but only 4 will have symp- ... adult ... males 4 will have movable kidneys but only

l will have symptoms. The diagnosis may be made by comparison of pyelograms in the upright and recumbent postures. Movable kidney is a disease of adult life. Fish and Hazzard found the following age distribution of 263 cases with symptoms: fifteen to twenty-nine years, 69; thirty to thirty-nine years, 96; forty to forty-nine years, 41; fifty to fifty-nine years, 30; over sixty years, 18 cases.

The disease is much more frequent in females. Kidd found sixteen times as many females as males with symptoms. Woodruff and Scherer 52 females and 33 males; Fish and Hazzard 221 females and 42 males; Mathé 72 females and 18 males; Morris, Sherman and Brunton 209 females and 41 males; and Birdsall 97 females and 53 males. It has been suggested that the preponderance in females is due to their having shallower renal fossa, with less fascial support at the lower pole of the kidney, the renal fossa in males being more pear-shaped. Few writers believe that pregnancy is an important etiological factor.

Movable kidney is much more frequent on the right side. Fish and Hazzard found 166 on the right, 25 on the left and 72 bilateral; Birdsall 76 right, 28 left, 46 bilateral; and Mathé 70 right, 11 lef 9 bilateral. It is thought that the more frequent displacement c the right kidney is due to the weight of the liver and weaker fascia support of the kidney.

Etiology. The etiological factors that have been suggested are (*a*) lax abdominal muscles following pregnancy or surgical operations, especially the removal of large abdominal tumors, or resulting from asthenia; (*b*) a narrow flat chest with downward displacement of the thoracic organs (Kidd); and weakness of the perirenal fascia. General visceroptosis is said to be infrequent.

Symptoms. The most characteristic symptom is pain in the region of the affected kidney, usually of a dull aching character but sometimes in the form of severe attacks like renal colic. The pain may be due to tension on the nerves in the renal pedicle, to acute passive congestion of the kidney, or to acute hydronephrosis or pyelonephritis. The pain is usually more severe in the upright than in the recumbent position. Nausea and vomiting are frequent symptoms. When the kidney becomes infected the symptoms of pyelonephritis appear, *viz.*, elevated temperature, chills, vomiting, pain and renal distention, leukocytosis, dysuria, etc. The attacks of renal colic may be accompanied by oliguria and followed by polyuria. When the kidney is infected pus is found in the urine. The displaced kidney is sometimes palpable.

Diagnosis. The diagnosis is suggested by the above symptoms, especially in a woman, but urograms are essential. All urologists emphasize the necessity of urograms in both the recumbent and upright positions in order to determine the amount of displacement of the kidney and the condition of its pelvis and ureter. Intra-

venous urograms are usually satisfactory but one may underestimate the degree of hydronephrosis Fish and Hazzard have published a number of good urograms Ectopic kidney is easily distinguished

ureter This may result from kinking of the ureter or from compression of it by a fibrous band or an accessory renal artery to the lower pole when the kidney is in the displaced position Sometimes there is a constricted ureteropelvic junction or a high insertion of the ureter in the pelvis

Pyelonephritis follows hydronephrosis frequently since the obstructed kidney is more susceptible to infection Ordinarily the kidney may be saved by appropriate treatment, but occasionally it

the asymptomatic group have put nephropexy into disrepute The milder cases which constitute a majority, may usually be relieved by medical treatment such as a belt and pad to hold the kidney up in position and exercises to strengthen the abdominal muscles Drainage of the infected kidney is sometimes necessary In 263 cases Fish and Hazzard cured 172 by non surgical treatment and 37 by nephropexy Nephropexy is best reserved for cases that do not respond to medical treatment Kidd does not do a nephropexy unless he can demonstrate fixation or kinking of the ureter in the urogram Surgery is usually indicated in cases complicated by calculus tumor or tuberculosis

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D ANOMALIES DUE TO FUSION

1 Horseshoe Kidneys —*In this anomaly there is fusion of the adjacent poles of the kidneys nearly always the lower poles across the median line Both kidneys are more median in position than normally and their pelves face more anteriorly* The fused organs

resemble a horseshoe with its concavity directed cranially. The kidneys are usually connected by a band of cortical tissue in which there is no external evidence of a line of separation. Sometimes the connection consists entirely of fibrous tissue. The pelves of the two kidneys are always entirely distinct. The ureters pass anteriorly across the lower parts of the kidneys. Beyer collected 18 cases from the literature in which the upper poles were fused, but in all of our 119 cases fusion was at the lower poles.

In the great majority of instances the horseshoe is symmetrically placed across the midline, but in 4 of our cases one kidney was smaller than the other and the fused organs were mainly on one side of the median line, exhibiting a transition to the unilateral fused kidney.

Botez (1912) found 72 horseshoe kidneys in 31,504 postmortems, 1:715. Guizzetti and Pariset (1911), 31 in 20,000, 1:645. In our 59,064 postmortems there were 119 cases, 1 to 497. Gutierrez estimates the frequency of horseshoe kidneys in urological examinations at 1:400.

In our group of 115 cases there were 21 stillborn infants and 14 infants under one year of age. The incidence in stillborn infants is 1 to 217. The incidence in persons over 10 years of age is 1 to 474.

Thompson states that horseshoe kidneys are found much oftener in males but gives no statistics. In the report of Guizzetti and Pariset the incidence in males is 1:618, in females 1:741. In our 119 cases there were 81 males and 38 females. The incidence in males is 1 to 463, in females 1 to 768. There is apparently a slight preponderance in males.

In the group of 35 infants there were 9 with some associated anomaly such as spina bifida and cleft palate, but in the group over one year of age there were no anomalies.

There is some evidence in the literature that horseshoe kidneys exhibit a high incidence of disease. Botez states that 52 of 120 collected cases had a serious renal disease.

Gutierrez believes that a great majority are diseased and that horseshoe kidney constitutes a clinical syndrome characterized by abdominal pain in the epigastric or umbilical region, chronic constipation, sometimes associated with gastrointestinal disturbances and urinary symptoms. Gutierrez' conclusions are not supported by our observations. In our 119 cases there were 7 with hydronephrosis, 3 due to calculi, 1 to carcinoma of the bladder, 1 to hypertrophy of the prostate, 1 to a metastatic tumor and 1 unexplained. There was 1 case of renal tuberculosis and 1 of chronic glomerulonephritis. In no instance could the lesion be attributed to the fact that the kidneys were fused. My observations do not support the view that horseshoe kidneys are more liable to disease than normal kidneys.

Horseshoe kidneys are explained embryologically as a result of

fusion of the renal blastemas This might occur from the eighth to the tenth fetal week when the lower poles are in close proximity

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2 **Unilateral Fused Kidney** —In this rare anomaly both kidneys lie on the same side of the vertebral bodies and are fused in various ways The most frequent type of fusion is the elongated kidney in which the ectopic organ is fused by its upper pole to the lower pole of the normally placed kidney (Fig 12) Commonly there is no caudal displacement but occasionally the elongated kidney extends into the pelvis Another variety is the L-shaped kidney in which the ectopic organ is hypoplastic and attached at a right angle to the lower pole of the orthotopic kidney Still rarer forms are the clumped kidney in which both organs are fused into an irregular mass medial fusion of the two kidneys the sigmoid kidney and a type in which the ectopic organ is placed above the orthotopic kidney

In all instances except the rare cases in which the renal mass lies in a central position on the vertebral bodies one ureter crosses the mid line The pelves are separate and the ureters open into the bladder in their normal positions so that the anomaly cannot be recognized by simple cystoscopic examination

The pelves nearly always face anteriorly There are usually several arteries which arise from the aorta or iliac arteries corresponding with the position of the kidney The ureters are sometimes tortuous or constricted because of unusual positions Stein, 1916 reviewed 58 cases and Kretschmer 1925, brought the number to 80 Mintz 1931 surveyed 100 cases and Pierson 1932 103 cases Boeminghaus 1932 collected 47 clinical cases 35 of which were recognized by pyelograms Beer and Lerber, 1937, collected 150 cases Wilmer 1938 made a thorough survey of the literature and collected 286 cases In 91 838 collected autopsies he found 12 cases about 1 7600 There is apparently no predominance of either sex The kidney was on the right side in 140 cases on the left in 90 The great majority of cases recognized clinically and at postmortem occurred in persons under fifty years of age

Symptoms and Diagnosis —Kretschmer estimated that less than one-half of the cases had symptoms Because of ureteral abnormalities there is frequently hydronephrosis in one or both parts of the kidney and this predisposes to pyelonephritis There is no increased

liability to any other renal disease. Because of its anterior position the fused kidney is often palpable and has been mistaken for a neoplasm; 4 instances are recorded in which this error led to total nephrectomy.

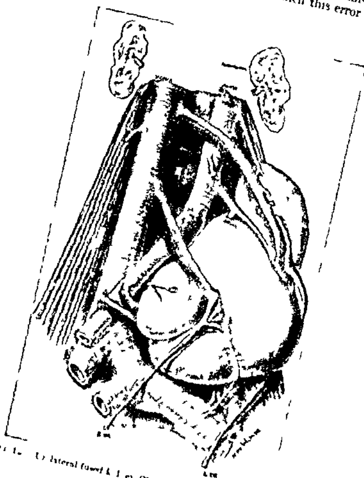


Fig. 1[illegible].—Unilateral fused kidney. (Widmer. Courtesy [illegible].)

In the event that hydronephrosis or pyelonephritis develops in one or both parts of the double kidney there is usually abdominal pain and often a palpable tumor sensitive to pressure. Pyuria, urinary frequency and fever are common symptoms. The cystoscopic examination does not reveal the nature of the anomaly since the ureteral openings are in their normal positions. The diagnosis

fusion of the renal blastemas This might occur from the eighth to the tenth fetal week when the lower poles are in close proximity

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Symptoms and Diagnosis —Kretschmer estimated that less than one-half of the cases had symptoms Because of ureteral abnormalities there is frequently hydronephrosis in one or both parts of the kidney and this predisposes to pyelonephritis There is no increased

ability to any other renal disease Because of its anterior position the fused kidney is often palpable and has been mistaken for a neoplasm 4 instances are recorded in which this error led to total nephrectomy

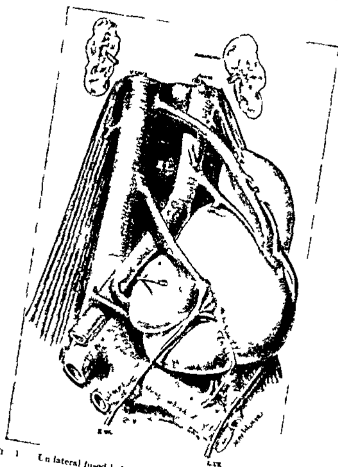


Fig 1 Unilateral fused kidney (Wilmer Courtesy of J Urol

In the event that hydronephrosis or pyelonephritis develops in one or both parts of the double kidney there is usually abdominal pain and often a palpable tumor sensitive to pressure Pyuria urinary frequency and fever are common symptoms The cystoscopic examination does not reveal the nature of the anomaly since the ureteral openings are in their normal positions The diagnosis

is readily made, however, from retrograde pyelograms with opaque catheters in the ureters in which the ureter may be seen crossing over to the ectopic kidney. Often only one of the two fused kidneys exhibits hydronephrosis or infection and the diseased kidney has been successfully removed in a number of instances (Rumpel).

In our 59 064 postmortems there were 11 cases of unilateral fused kidney, 1 to 5370. These will be described briefly.

28-858.—A stillborn male infant. Ectopic unilateral fused kidney in the right side of the pelvic cavity. The displaced left kidney was about one-fourth the size of the right and fused to its lower pole. The ureteral openings in the bladder were normal.

35-699.—A stillborn male infant. Fused kidney on the right side, the upper pole of the ectopic left kidney being fused to the lower pole of the right.

38-2569. Male, aged fifty-eight years. Death from primary hyper [illegible]

[illegible]

at uretero-pelvic junction. Normal ureteral openings in the bladder. Chronic glomerulonephritis.

[illegible]

into the bladder.

44-1423. An infant, aged one week. There was a fused kidney on the right side in the normal position of the kidney, from which two ureters arose and opened into the bladder normally. There were no gonads or genital organs.

46-1536.—A male 4[illegible] years of age. Death from cirrhosis of the liver. The displaced right kidney was attached by its upper pole to the lower pole of the normally placed kidney. The elongated kidney weighed 380 gm. and exhibited no disease.

46-2142. A female 72 years of age. Death from lobar pneumonia. The displaced left kidney was attached at a right angle to the lower pole of the right. Three renal arteries were present. The kidney mass weighed 2[illegible]0 gm. and showed no disease.

47-777.—A stillborn female. The displaced left kidney was attached at a right angle to the lower pole of the right. No disease was present.

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E DUPLICATION OF PELVIS AND URETER

In a study of over 60 human embryos Pohlman found complete double ureters in 2 embryos under the third month. To explain the double ureter embryologists usually assume that the ureteral bud is either completely split or it grows out as two separate buds. Pohlman explains incomplete double ureter as a result of premature branching of the ureteral bud. When the bud is incompletely fissured the two ureters join at some point and continue to the bladder as a single trunk.

The duplication of the ureter may be bilateral or unilateral and complete or incomplete. Analysis of our 302 cases shows 47 bilateral and 255 unilateral. The unilateral form is over 5 times as frequent as the bilateral. Braasch and Scholl found only [illegible] per cent of 144 clinical cases to be bilateral but Mertz found 27 per cent of 300 cases bilateral. Our 47 bilateral cases are subdivided as follows: complete bilateral duplication (4 complete ureters) 12 cases, complete duplication on one side and incomplete on the other 4 cases, incomplete duplication on both sides 27 cases, and undetermined degree of splitting on both sides 4 cases.

Our 255 unilateral cases are subdivided into complete unilateral duplication (3 ureters) 51 cases, incomplete splitting 182 cases, and undetermined degree of splitting 22 cases. Incomplete splitting is over three times as frequent as complete splitting. Braasch and Scholl in 144 clinical cases found 30 per cent complete and 70 per cent incomplete.

In bilateral complete splitting there are four openings into the bladder, in complete unilateral there are three, and in any form of incomplete splitting there are only two. In both complete and incomplete duplication there is a double pelvis. In the incomplete type the two ureters join at any point between the pelvis and the bladder and proceed the rest of the way as a single ureter. In about half of the cases the ureters join in the lower third just above or within the wall of the bladder; in the other 50 per cent union takes place in the upper or middle third. Bugbee and Losee described instances of duplication involving the lower end of the ureter only, but others have doubted this observation.

As in unilateral agenesis the left side is involved somewhat more

frequently than the right. In our 255 unilateral cases 145 were on the left side and 110 on the right.

Ureteral duplication is definitely more frequent in females in our experience. Of 302 cases there were 144 males and 158 females. This gives an incidence in males of 1 to 200 and in females of 1 to 130.

The frequency of pelvic and ureteral duplication is difficult to determine from postmortem statistics since the anomaly is easily overlooked unless special attention is directed to it. Our own observations, 302 cases in 59,064 postmortems or 1 to 195, are no doubt incomplete and give too low an incidence. More accurate is Motzfeldt's report of 12 cases in 972 postmortems in which special note was made of the ureters. Bostroem found 19 cases in 639 postmortems. Cases with complete duplication are readily recognized on cystoscopic examination, more than two ureteral openings being present. Geisinger in 500 cystoscopies found 1.4 per cent with more than two ureteral orifices and Culver found 1.3 per cent in 600 cystoscopies. If we assume that incomplete duplication is three times as frequent as the complete type, these cystoscopic data indicate an incidence of some type of double ureter in about 4 per cent of the population, but this may be too high since the complicating infections bring a larger percentage of this group to the urologist. Frequently union of the ureters takes place in the wall of the bladder. At postmortem examination it is necessary to examine the bladder to determine whether the duplication is complete.

Ectopic Ureteral Opening. In cases of complete ureteral duplication one of the ureters sometimes opens outside the bladder. Mertz found an ectopic opening in 30 per cent of 140 cases of complete ureteral duplication and Braasch and Scholl found 3 in 44 such cases. There were only two ectopic ureteral openings in our 67 cases of complete duplication.

In the female the ectopic ureter usually opens in the vestibule near the urethral meatus but often in the urethra. There is usually a continuous dribbling of urine with wetting of the vulva and perineum. The ectopic ureter is commonly connected with an atrophic hydronephrotic upper segment of the kidney which has a low functional capacity but secretes a watery urine of low specific gravity. In the cases in which there is no dribbling of urine the symptoms are those of obstruction or infection of the upper urinary tract. It is necessary to do a heminephrectomy or a nephrectomy.

In the male the ectopic ureter opens into the prostatic urethra, seminal vesicles, vas deferens or ejaculatory duct. There is no dribbling of urine and the symptoms are those of hydronephrosis or renal infection. The lesion is usually recognized clinically in females but seldom in males. Thom surveyed 210 cases with extravesicular ureteral openings.

The kidney with a double pelvis is often longer and heavier than normal, but there may be no change in its shape or size. On external inspection there may be no indication of a separation between the two segments, but often there is a depression or a deep groove between the upper and lower segments, and rarely they are connected only by a fibrous cord (Hawlisch). On mid sagittal section it is noted that the two pelves are always entirely distinct but the cortical tissue of the two parts is intimately fused. Sometimes an indefinite line of separation is seen between the two kidneys (Fig. 13). The upper segment is the smaller. The number of pyramids in the double kidney is often somewhat greater than the average normal.

Mertz found pathological complications in 80 of 300 cases, Braasch and Scholl in 54 of 144. It is to be remembered, however, that the urologist sees a highly selected material; the patient comes to the urologist because of complications. Minder stated that only 3 per cent of cases found at postmortem have had symptoms. In our 302 cases there were 33 with a renal lesion of some kind, but many of them were not due to the presence of the anomaly. The unrelated lesions were: miliary tuberculosis, 1 case; multiple abscesses, 2; pyelonephritis without involvement of the ureters, 1; hydronephrosis due to a pelvic tumor, 3; hydronephrosis due to prostatic hypertrophy, 1; calculi without hydronephrosis or infection, 1; and bilateral pyelonephritis with calculi in a case with incomplete unilateral duplication, 1.

There remain 23 cases in which the lesion was directly attributable to the presence of the anomaly, an incidence of about 8 per cent. There were 7 instances of hydronephrosis of the upper segment of the double kidney. Two of these were complete duplication with obstruction in the bladder from an enlarged prostate in 1 and from atresia in the other. The other 2 were examples of incomplete splitting with atresia at the point of union of the ureters.

There were 4 instances of hydronephrosis of the lower segment, 3 due to ureteral atresia and 1 to calculi. In 8 cases there was hydronephrosis of both upper and lower segments from ureteral atresia and in 2 cases one segment was dilated (upper or lower not stated).

There were only 4 deaths due to the anomaly. Three deaths were due to hydronephrosis and pyelonephritis. The other was a case of complete ureteral duplication on the right side in a child four months old. One of the double ureters was closed by a membrane in the mucosa of the bladder. A ureterocele developed which obstructed the other two ureteral openings and caused uremia.

There were 3 cases of solitary kidney without any renal lesion. In 1 of these the two ureters opened in the usual positions in the bladder so that cystoscopic examination would have indicated two

normal kidneys. There were four horseshoe kidneys without disease.
The double kidney is therefore not predisposed to any disease except hydronephrosis and the infection that may subsequently develop. Obstruction is due to ureteral stenosis or atresia which may be found at the point of junction of the ureters in incomplete splitting or in the wall of the bladder in complete duplication.

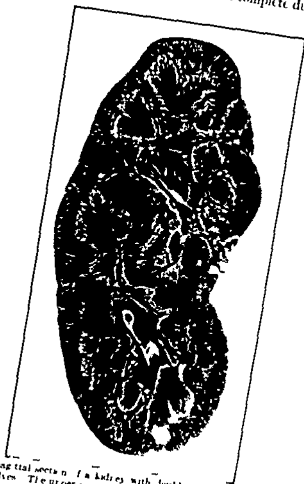


FIG. 13. Mid-sagittal section of a kidney with double ureter. Note the separate pelves. The upper segment is the smaller. Photograph.

When symptoms are present they are referable to hydronephrosis or pyelonephritis and are not different from the symptoms which these diseases produce in a kidney with a single pelvis. One segment of a double kidney may develop calculi, tuberculosis or a neoplasm when the other segment is normal. In favorable cases a heminephrectomy may be performed. Hellström (1927) collected

28 reports of heminephrectomy Usually it is necessary to remove the entire kidney Braasch and Scholl did 15 nephrectomies and 4 heminephrectomies

The diagnosis of ureteral duplication may be made from cystoscopic examination in cases of complete duplication from the presence of more than two ureteral orifices A pyelogram is necessary to demonstrate incomplete duplication One branch of the forked ureter sometimes does not fill when the medium is introduced from below but the shape of the injected pelvis usually leads to the correct diagnosis in these cases Intravenous pyelography is usually satisfactory When one segment does not excrete the size and shape of the pelvis suggests the correct diagnosis

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F CYSTIC DISEASE OF THE KIDNEYS

In a majority of adult kidneys one or more microscopic cysts are found which may reach a diameter of several centimeters One also sees enlarged kidneys filled with cysts but still containing sufficient parenchyma to maintain normal function I have used the term subclinical to designate this latter group The clinical group is characterized by great enlargement of the kidneys and large numbers of closely packed cysts with only small scattered islands of persisting parenchyma Solitary cysts may produce symptoms when sufficiently large or when infected

A convenient classification of renal cysts is as follows

1 Cystic disease (typical polycystic kidneys)
   a Bilateral polycystic kidneys)
      i Clinical
      ii Subclinical
   b Unilateral polycystic kidney
2 Large solitary cysts
3 Multiple small cysts associated with contracted kidneys

Frequency —The incidence of polycystic kidneys in postmortem examinations varies greatly in different reports Combined statistics from the literature show 313 cases in 110 024 postmortems 1 351 The frequency of polycystic kidneys in postmortems depends in part upon whether the subclinical and unilateral groups are included some writers including kidneys only partially replaced by cysts The frequency is also influenced by the number of stillbirths and young infants that are included in the series In our 59 064 postmortems there were 100 clinical cases 1 590 If the 17 subclinical and the 14 unilateral cases be included the incidence is 1 450 In 4512 stillbirths there were 14 cases (1 322) and there were 19 other cases in infants under six months of age In 54 512 postmortems on individuals over 10 years of age there were 70 clinical cases 1 779

Not infrequently at autopsy one kidney is normal and the other indistinguishable from the bilateral polycystic type except that it is not so large The unilateral cystic kidney is often hypoplastic Such hypoplastic kidneys have been described by Schafer Herxheimer Baumann Rosenow and others I have 16 such cases (Table 2) but have preferred to classify them as hypoplastic kidneys since hypoplasia is their most salient feature

Sieber stated that 9 of 150 collected cases were unilateral Wakely reported a unilateral cystic kidney measuring 7 x 5 inches in a child twenty months old Lejars found 3 of 62 cases unilateral Ritchie 2 of 88 Naumann 2 of 16 and Bugbee and Wollstein 4 of 15 Dickenson thought that about 4 per cent were unilateral while Luzzatto found 18 per cent unilateral Fourteen of our cases were unilateral Including our cases 34 of 447 polycystic kidneys were unilateral—an incidence of about 8 per cent Some writers doubt the existence of the unilateral type but it is well established that it occurs in adults as well as in infants The clinical reports of unilateral disease are considered unreliable because it is known that one kidney may enlarge much faster than the other and attain an enormous size before its mate is palpable Several instances have been published in which a supposedly normal kidney has become large and polycystic many years after the removal of its polycystic mate

In our experience unilateral polycystic kidneys are much smaller than the bilateral type the largest example weighing 666 gm

(Table 8), but the destruction of the parenchyma is just as complete
In all
mate
the 7
trophy.

Bilateral Polycystic Kidneys

Age —In all studies of polycystic kidneys the recorded age represents either the age at death or the age when symptoms first appeared, and on this basis it has long been recognized that the cases are observed at two periods, *viz*, early infancy and adult life, and

before the third decade A search of the literature, however, shows that a number of cases in the first and second decades have been recorded In Kuster's table there are 6 cases between the ages of one and five years, 1 between five and ten years and 4 between ten and twenty years Albarran and Imbert, 1903, col-
twenty years,
In Willan's
age of a few
months, symptoms appeared at the age of seventeen years, and death from uremia occurred at the age of thirty-one years Rossen's patient developed symptoms at the age of nine years and died

TABLE 7 —AGE DISTRIBUTION OF POLYCYSTIC RENAL DISEASE

Age group	Autopsy cases				Cases from literature
	Clinical	Subclinical	Unilateral	Total	
Stillborn	10	0	4	14	28
0 1 mo	15	0	1	16	6
1–6 mo	3	0	0	3	6
6 mo – 1 yr	2	0	1	3	6
1 5 yr	0	0	0	0	18
5 10 yr	0	0	0	0	4
10 20 yr	0	0	0	0	19
20 30 yr	2	2	0	4	22
30–40 yr	11	2	0	13	42
40–50 yr	16	0	2	18	74
50–60 yr	18	3	0	21	51
60 70 yr	16	4	2	22	15
70–80 yr	3	1	2	6	4
80 90 yr	2	5	1	8	2
Adult	2	0	1	3	0
	100	17	14	131	297

hypertension hematuria and a typical pyelogram. These cases in children and adolescents serve to bridge the gap between the infantile and adult types. In Table 7 the age distribution of 297 cases collected from the literature is shown. This is only a small fraction of the total literature but perhaps the group is sufficiently large to show the general age distribution. No doubt the number of stillbirths is much too small in proportion to the other groups since these cases are seldom published. The number in children and adolescents is proportionately too high since these are of great interest. A more accurate picture of the actual distribution is shown in our autopsy series (column 4, Table 7). The infantile group comprises 36 of our 131 cases.

Why do so many children die in infancy and why are there so few clinical cases between infancy and adult life? We have no satisfactory answer to these questions. We know that the disease begins in the prenatal period and that many of the infants are stillborn because of polycystic disease or other associated anomalies. Of those born alive we may believe that some cases are severe and others mild at birth, that the former die in early infancy and the latter continue to live until the disease has progressed to the point of renal insufficiency. To explain the infrequency of clinical cases in childhood and adolescence we may believe either that the cysts do not increase in size greatly during this period or that hypertrophy of parenchyma between the cysts is a compensatory factor. The fact that frequently in adults the kidneys increase greatly in size during several years of observation supports the former theory, or that the rate of growth of the cysts is the important factor. For some unknown reason the cysts may remain latent for years and then begin to increase in size. Lambert believes that in the newborn type the cystic nephrons do not communicate with the pelvis.

Sex.—Large statistics indicate that there is no difference in the incidence in males and females. Braasch and Schacht had 98 females and 95 males in their group of 193 patients. This is more accurate than postmortem statistics since there are more autopsies on males than on females. In our group of 131 cases there were 81 males and 50 females, an incidence of 1 463 in males and 1 132 in females.

Clinical Features. The symptoms and findings vary with the stage of the disease and are also influenced by the development of infection or hematuria or by the enlargement of one kidney in advance of the other.

(a) *Early Stage.* In the early stage, before any symptoms have developed the disease may be recognized by the finding of palpable kidneys but the kidneys are frequently not palpable before the onset of symptoms. Several investigators having recognized a clinical case studied other members of the family who had no

symptoms. Often the disease is recognizable by the abnormal pyelogram in the absence of symptoms.

(b) *The Surgical Type.* Often the initial symptoms are those of a unilateral renal disease. There may be a palpable kidney with localized pain and tenderness, fever and leukocytosis, or there may be attacks of hematuria with the blood coming from one kidney only. When both kidneys are palpable the diagnosis is usually clear, but when only the affected kidney is palpable an incorrect diagnosis may be made unless satisfactory pyelograms are obtained. If the attacks of pain associated with hematuria are like renal colic they are probably caused by ureteral spasm during the passage of blood clots. Occasionally one or more cysts become infected giving rise to pyuria and other symptoms of pyelonephritis. When the function of the two kidneys is studied separately it is sometimes found that the blood and pus come only from one kidney and that it excretes little or no indigo carmine while the function of the opposite kidney is good. Under these circumstances it may be justifiable to remove the non functioning kidney. A great many writers are opposed to nephrectomy under any circumstances particularly because the disease is bilateral but there are some reports in which nephrectomy was followed by a long period of relief. Blatt's patient was living fifteen years after nephrectomy and the other kidney was not palpable until twelve years after the operation. Rumpel's patient was living and well twelve years after removal of a polycystic kidney which excreted no indigo carmine. In a case reported by Blum pain developed in the region of the left kidney at the age of fifteen years. The pain continued and the patient had frequent attacks of hematuria until the age of twenty-one years when the left kidney was removed since its function was very poor while that of the right was normal. Twelve years later at the age of thirty three years the right kidney first began to enlarge and become painful. The patient was living seventeen years after the nephrectomy. Walters and Braasch recommend nephrectomy when one kidney shows infection with a marked reduction of function provided the function of the other kidney is good. They reported 31 nephrectomies. Some of the cures following nephrectomy may be examples of the unilateral type of the disease.

When kidneys are removed from patients presenting symptoms of unilateral pyelonephritis they usually show one or more cysts filled with pus and one of the infected cysts may have ruptured into the renal pelvis. Kidneys which exhibit chiefly pain and hematuria show some cysts filled with blood which have ruptured into the pelvis.

(c) *The Uremic Type.* A majority of persons with polycystic kidneys come to the physician with symptoms referable to renal insufficiency. The clinical picture is often similar to that of chronic glomerulonephritis. The onset of uremia may be sudden but more often it develops slowly over a period of years. The patient may

complain of weakness, vague abdominal pain, vomiting or abdominal distention. Frequently there is a well-defined syndrome of renal disease with hypertension and renal insufficiency.

Albumin is found in the urine from a trace to a large amount in the great majority of cases (180 of 190, Braasch and Schacht). This is probably due to interference with the blood supply of the glomeruli from pressure of cysts and from stretching and compression of arteries and veins, there is no recognizable disease in the glomeruli.

TABLE 8.—UNILATERAL POLYCYSTIC KIDNEYS

Serial no	Autopsy no	Age	Sex	Blood pressure	Weight of heart, gm	Weight of kidneys, gm R	L	Cause of death
1	37-2258	SB	M		11	37*	11.5	
2	30-1811	SB	F			10	33*	
3	37-418	SB	F		Norm	Cystic* enlarged	Norm	
4	37-646	SB	M		14.5	10	10*	
5	20-260	6 mo	M			73*	8.5	
6	28-1732	45	F	195/110	325	500*	210	Carcinoma of stomach
7	34-957	65	F	160/100	499	177	660*	Cardiac failure, cerebral hemorrhage
8	35-1478	66	M	180/88	5[illegible]0	150	105*	Coronary sclerosis
9	36-1814	87	M	150/100	580	215	325*	Cardiac failure
10	38-374	76	F	172/92	270	270*	135	Coronary sclerosis
11	38-2316	Adult	M	180/150	600	550*	185	Hypertension, cardiac failure
12	46-1511	79	M	180/100	435	460*	140	Coronary sclerosis
13	47-189	41	M	210/120	490	60*	110	Cerebral hemorrhage
14	47-2022	20 min	M		18	2	10*	

* Indicates cystic kidney

TABLE 9.—CLINICAL POLYCYSTIC KIDNEYS IN ADULTS

Serial no	Autopsy no	Age	Sex	Duration of symptoms	Functional tests	Cystic liver, gm	Blood pressure	Weight of heart, gm	Weight of kidneys, gm	Cause of death
1	27-308	27	F	?	Indigo-carm. 0 20 min, pep. 3%, n.n. 15.6	0	[illegible] 52, 3 wk	240	830, 8[illegible]1	Bact. endocarditis
2	30-458	66	F	5 yr	?	0	194/96	230	[illegible]	Pyelonephritis
3	30-1790	Adult	M	?	?	2650 +	?	440	430, [illegible]	Postoper shock
4	31-139	44	F	2 yr	"	+	?	?	[illegible]	Postoper infection
5	33-351	52	M	"	?	0	?	440	[illegible]	Fracture of skull
6	34-63	33	F	3 yr	?	+++ 3510	?	330	[illegible]	Postoper shock
	32-146	64	F	?		0	210/130	255	231, 275	Uremia

TABLE 9.—CLINICAL POLYCYSTIC KIDNEYS IN ADULTS—(*Continued*)

Serial no.	Autopsy no.	Age	Sex	Duration of symptoms	Functional tests	Cystic liver gm.	Blood pressure	Weight of heart gm.	Weight of kidneys gm.	Cause of death
8	25 297	45	F	2 mo	Sp gr 1.010	0	90/50 1 da	292	847 663	Uremia
9	26-699	59	M	10 yr	?	++	124 84	250	very large	Uremia
10	28-1309	49	M	3 wk	u n 118	0	?	335	520 545	Uremia, glioma
11	29 1159	25	M	3 yr	u n 174 psp 0	0	165/110	420	840 1240	Uremia
12	34 623	48	M	2 yr	npn 163 7	0	144 84	550	1400 960	Uremia
13	18-310	42	F	?	?	0	?	?	1250 1290	Uremia
14	23-92	39	F	6 wk +	?	0	?	?	1300 2500	Uremia
15	31 1150	58	F	10 yr	?	0	235/110	470	1100 1570	Uremia
16	31 2054	68	F	2 yr +	u n 142 9	0	248/140	375	1450 2150	Uremia
17	33 299	40	M	3 mo.	u n 109 9	0	190/134	560	2600 1800	Uremia
18	33 1540	40	M	3 yr +	?	0	High	430	1973 2590	Uremia
19	34-841	57	F	2 mo +	u n 234	++	170/110	275	650 900	Uremia
20	35-977	36	M	?	?	0	?	800	3225 2450	Uremia
21	36-1142	47	F	10 yr +	No indigo-carm.	+ 2300	High (10 yr)	300	1550 2750	Uremia
22	36-1436	51	M	8 yr	u n 117	0	154 100 180 90	450	2100 (2)	Uremia
23	36 1459	66	M	19 da	?	0	120/60 (17 da)	400	600 1700	Uremia
24	37-622	30	M	6 mo	u n 231	0	106/76 146/70	300	370 360	Uremia
25	37-634	57	F	6 yr	u n 62 (2 mo	1850 +	174 108 230 120	450	1975 1325	Uremia
26	37 2358	52	M	3 yr	u n 60 (1 wk)	1900 +	170/100	400	1675 1415	Uremia
27	38 241	63	F	1 yr	u n, 170 3 da.	2350 +	132/74 (2 wk)	475	1700 1075	Uremia
28	39-499	56	F	10 yr	u n 9 (10 yr) u n 125 (1 mo) psp 15 (3 yr)	5370 +++	155/80 (10 yr) 190/100 (3 yr)	260	1550 1120	Uremia
29	38 1321	61	M	6 wk	u n 114	3350 ++		500	2000 2500	Uremia
30	38 1078	69	M	2 yr	u n 75	1920 +	196/100 4 yr 174/78 1 wk	615	635 475	Uremia cardiac failure
31	39-4	50	F	?		1900 +	100/70 3 da	275	600 700	Uremia?
32	39-1156	69	F	2 yr	u n 72 3 (3 wk)	0	240/120	690	120 300	Uremia
33	39-2167	63	F	Many yrs	u n., 175	0	164/90	400	1400 1170	Uremia
34	39 2602	49	F	?	?	0	?	450	1200 1200	Uremia
35	40-528	40	M	6 mo	psp 0%	0	120/100	350	2300 1300	Uremia
36	40-2368	52	M	Many yr	u n 104	+ 2010	155/115	365	1000 900	Uremia
37	41-859	49	M	7 wk		+	206/130	450	3150 2900	Uremia
38	41 897	38	M	No symptoms		0	?	390	720 730	Coronary sclerosis
39	41 1355	47	M	4 mo.	u n., 155	+ 1900 gm.	128/90	310	1200 1150	Uremia
40	41 2094	54	F	?	u n., 34	0	196/100	250	(both) 1500	Encephalomalacia
41	41 2164	61	M	5 yr	u n 189	+ 2675	190/98	415	565 500	Uremia
42	42 233	54	M	1 yr	u n 114	+ 1900	210/110	500	860 1170	Uremia
43	42 2310	50	M	6 yr	u n 35	0	?	500	large 1250	Nephrectomy for renal calculi

Fahr suggested that cases of polycystic disease without hypertension were those in which the parenchyma was not so extensively atrophied. Braasch and Schacht found a somewhat higher incidence of hypertension in the more advanced stages of the disease and several writers in studying individual cases over a period of years have noted a gradual rise of blood pressure. A progressive rise of blood pressure over a period of several years was noted in 4 of our cases. There is no doubt that atrophy of the renal parenchyma and renal insufficiency resulting from the progressive enlargement of the cysts usually causes an increase of blood pressure but some patients dead of uremia showed neither hypertension nor cardiac hypertrophy (Nos 39 and 42 Table 9).

Hypertrophy of the Heart.—In the literature we have found the weight of the heart recorded in only 8 adults, the average weight being about 470 gm. In 7 cases it was described as hypertrophied and in 4 as not enlarged, no weights being given.

In our clinical cases in adults the weights of the hearts in 67 cases were as follows: 200 to 250 gm, 4; 251 to 300 gm, 12; 301 to 350 gm, 9; 351 to 400 gm, 9; 401 to 450 gm, 14; 451 to 500 gm, 7; over 500 gm, 12 cases. Cardiac hypertrophy occurs frequently in polycystic renal disease but it is not so constant and pronounced as it is in primary hypertension. Death from cardiac failure seems to be unusual; in only 1 of our cases (No 30) was there definite clinical evidence of cardiac decompensation but in several instances a slight passive congestion of the liver was found at postmortem. Rivoir described an instance of death from cardiac insufficiency in a male aged sixty five years with very large polycystic kidneys. Sieber had 2 cases in which death was due to cardiac failure. In our group there were 5 deaths attributed to coronary sclerosis.

Renal Insufficiency.—The majority of the symptoms in polycystic renal disease are due to renal insufficiency and resemble those occurring in chronic glomerulonephritis. There may be gastrointestinal symptoms such as loss of appetite, nausea, vomiting, constipation or diarrhea. Anemia and weakness are common and there may be marked loss of weight. Periods of malaise and headache occur. A definite impairment of renal function is demonstrable in about two-thirds of the patients when they first consult a physician. There is a decreased elimination of phenolsulphonephthalein comparatively early in the disease and there is also a decrease of the ability to form a concentrated urine. Later there is a rise of blood urea and creatinine and these substances may be markedly increased for many months before death. Chronic uremia occurs much oftener than the acute form.

The functional tests reveal the amount of functioning parenchyma and do not indicate the nature of the disease or the part of the nephron that is affected. Death is usually due to uremia but may result from infection of the cysts or from some other lesion.

Cerebral Hemorrhage —Sieber in his survey of the literature in 1901 found that 10 of 212 patients died of cerebral hemorrhage Dunger reported the death of a woman aged fifty four years from a ruptured aneurysm in the corpus callosum Her daughter died at the age of twenty six years from a pontine hemorrhage Blatt noted death from cerebral hemorrhage in a woman forty-six years old McKinlay described an intracranial hemorrhage in a male thirty years of age One of our patients a male aged forty years suffered a hemiplegia at the age of thirty seven years but died of

rupture of arteriosclerotic blood vessels in the brain There were two deaths in our gr up from subarachnoid hemorrhage

Duration of Symptoms —Braasch and Schacht found that 45 per cent of 193 patients lived less than four years after the onset of symptoms Twenty five lived more than ten years and 9 more than twenty years
authors Blatt (eigl

years)
nts had
disease
depends to some extent upon the effort made to establish the diagnosis in the early stages since it is congenital but some patients do not have symptoms that attract their attention until a few months before death

The onset of symptoms may be dated from (*a*) the discovery of a palpable kidney (*b*) an infection developing in a cyst and causing symptoms of pyelonephritis (*c*) hematuria (*d*) albuminuria and (*e*) any of the various symptoms of renal insufficiency

Retinal Changes —The retinal changes in polycystic renal disease are not well known since it is not always clear what the authors mean by retinitis Apparently the fundi are normal in about 50 per cent and in a great majority of the remainder the only change is narrowing of the retinal arteries Retinitis in the sense of hemorrhages and exudates occurs infrequently As in other forms of renal disease the retinal changes result from the high blood pressure

The Pyelogram Pyelography is a most valuable aid in diagnosis especially when only one kidney is enlarged and when neither kidney is greatly increased in size When renal function is poor intravenous pyelography is unsatisfactory since the kidneys do not

and the calices are stretched out, widened and rounded. When the kidney is small the picture is not so convincing (Fig 14). Often pyelography is the only means of establishing the diagnosis.

Effects of Pregnancy — Pregnancy increases the work of the kidneys and not only intensifies any preexisting symptoms but may also bring out symptoms in a latent stage of the disease. Blatt described a patient aged thirty-eight years, who first developed



Fig 14 Bilateral polycystic kidneys. Retrograde pyelogram. Note the elongation and deformity of the renal pelvis

symptoms during pregnancy. There was marked edema, albuminuria and vomiting. The child was born at eight months, and for one year afterwards there was general weakness, albuminuria and headache. The patient then remained well for five years, after which the symptoms reappeared. Sieber observed 2 patients in whom the first symptoms developed during pregnancy.

A patient reported by Heinsius developed marked edema, heavy

albuminuria, visual disturbances and severe dyspnea during the seventh month of pregnancy. At postmortem abscesses were found in the large cystic kidneys.

However, symptoms do not develop during pregnancy unless the disease is well advanced. Seitz reported a woman who had 7 pregnancies and Wagner one with 12 pregnancies without complications. In Podgurski's case the patient went through 13 pregnancies and first developed renal symptoms at the age of seventy-three years. In 1 of our cases (No. 2, Table 9) the patient bore 14 children and first developed symptoms at the age of sixty-one years. Death resulted from a complicating pyelonephritis at the age of sixty-six years; uremia had not developed. The kidneys at postmortem were not very large and there was a fair amount of normal parenchyma. There are numerous reports in the literature of women having borne one or more children before the onset of symptoms. Duskes reported a woman forty-five years of age who had had 10 full term pregnancies and 4 miscarriages. Death was due to uremia. Strubing's patient, fifty-one years of age, had 5 children and 7 abortions. Six years after the birth of the last child symptoms appeared.

Heredity.—It has been known for many years that heredity plays a major role in polycystic renal disease. Families with a high incidence of the disease have been reported by Dunger, Paus, Cairns, Fuller and Shapiro. Dunger (1904) found the disease in 5 children of the same mother. In addition he observed the disease in a mother aged fifty-four years and in her daughter aged twenty-six years. Paus (1914) in the family which he studied found 4 members in the first generation, 2 of whom had cystic kidneys. One of those with cystic kidneys had 14 children, of whom 4 had cystic kidneys; the other with cystic kidneys had 3 children, none with the disease. One of the normal members of the first generation had 4 normal children but a granddaughter had cystic kidneys.

Cairns (1925) noted 10 cases in 3 generations of a family. Fuller (1929) described 9 cases in 27 members of a family in 4 generations. Shapiro (1929) found the disease in a mother, in 4 of her children and in 1 of her grandchildren. Cannon illustrates a large family in which polycystic kidneys appeared in four generations.

In addition to these larger groups a great many writers have called attention to more than one case in a family. Beck (1901) reported 3 sisters with polycystic renal disease. Bunting (1906) found the disease in 2 newborn children of the same mother. Wobus (1918) found 4 children of the same mother with polycystic kidneys. Rumpel (1921) found two families each with 3 cases of cystic kidneys in 2 generations. Cumming (1928) found a familial history of the disease in 11 of 31 cases which he studied. Halbertsma (1931) found the disease in a man forty years old and his daughter ten years of age. Balogh (1933) reported 3 cases in the first generation of a family and 3 in the second. A great many observations

similar to those mentioned have been published Maier 1924 quoted 24 writers who had found examples of hereditary polycystic kidneys and Bunting al o gave a number of references It is clearly established that heredity is the most important factor in the etiology The tendency to the anomaly may be transmitted by either sex and apparently it is carried by a dominant gene It is not known whether persons without symptoms who transmit the disease to their offspring have normal kidneys or a subclinical form of cystic kidneys

early stages Braasch and Schacht in 193 patients found bilateral

intestines or other structures but for the most part the symptoms are referable to renal insufficiency and do not differ essentially from those associated with chronic glomerulonephritis but hypertension and retinitis are absent more frequently than in glomerulonephritis A moderate edema of the lower extremities is occasionally seen but marked edema is very unusual Cardiac decompensation seems to be uncommon Attacks of hematuria are suggestive of polycystic kidneys

The cases in which only one kidney is enlarged present diagnostic difficulties When a calculus is demonstrated as happens occasionally the nature of the underlying disease may be overlooked It is not unusual to find a marked difference in the size of the two ... they may al o exhibit ... disease is demonstrable ... ys that it is unilateral In a case reported by Blum the right kidney first showed a demon...

out the characteristic shape of the pelvis as revealed by the pyelogram the accuracy of the clinical diagnosis has improved markedly The most convincing pictures are obtained on large kidneys the typical appearance being elongation of the pelvis and calices The calices may be widened especially at their tips or one or more of them may be flattened or obliterated (Fig 14) The lengthening of the pelvis and calices is due to the increased size of the kidney and their distortion is due to encroachment of cysts upon them In small kidneys the diagnosis may be uncertain

Pathology —Polycystic kidneys retain the shape of a normal

kidney the various dimensions being increased proportionally There may be some displacement caudally because of the increased weight When very large the kidneys fill the lateral retroperitoneal areas displacing the intestines anteriorly and medially

The external surfaces are closely set with rounded elevated areas corresponding to the underlying spherical cysts On section a honeycomb appearance is noted In advanced cases the cysts are separated only by narrow bands of tissue and little or no normal parenchyma is to be seen (Fig 15) Occasionally in advanced cases

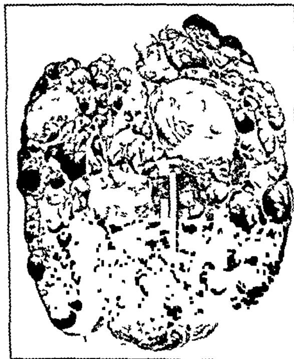


Fig 15 Large polycystic kidney in sagittal section Note large areas of persisting parenchyma at the center and a few small areas elsewhere Photograph

small islands of parenchyma 1 cm or more in diameter are found and in cases in which death was not due to renal insufficiency there may be large amounts of parenchyma between the cysts (Fig 16) When the parenchyma is reduced to a minimum the persistent portions are usually in the subcapsular zone Usually both cortex and medulla are filled with cysts and no separation between these portions can be seen but in rare instances there are no cysts in the medulla Schaefer described a kidney with a row of cysts at

the cortico-medullary junction and none elsewhere One pole of the kidney may be filled with cysts and the other pole normal (No 4 Table 8) In the smaller kidneys all the cysts may be small and of uniform size giving the parenchyma a spongy texture In infants the cysts are often of this character (Fig 17) In adults the cysts are usually larger and show great variation in size In general there is a direct relation between the size of a kidney and the size of its cysts and one gets the impression that enlargement is due to increase in the size of the cysts rather than to increase in their number



Fig 16 Subclinical polycystic kidney Note large areas of persisting parenchyma This [illegible] did not [illegible] uremia [illegible] Photograph

Frequently some of the cysts communicate with the calices When hematuria occurs it is commonly due to bleeding within a cyst that communicates with the pelvis The cysts are filled with a watery fluid which is usually clear but sometimes colored brown black or red from admixture of old or fresh hemorrhage Chemical examination reveals a high content of urea uric acid and creatinine In Piersol's case the fluid from the cysts contained uric acid 20 mg creatinine 28 mg and urea nitrogen 300 mg per 100 cc Litzner found urea 321 8 mg and uric acid 12 6 mg per 100 cc In both of these cases there was a marked retention of nitrogen in the blood corresponding roughly to the content of the cystic fluid

Singer and Brams found 45 9 mg of urea per 100 cc in the cystic fluid of a newborn infant Strubing found serum globulin as well as urea in cystic fluid from cases without renal insufficiency

Bilateral Cystic Kidneys in Infants —In the group of newborn infants there is an enormous variation in the size of the kidneys In the 30 cases in our series the combined weight of the kidneys aried from 40 to 974 gm About two-thirds of the infants were orn prematurely from the sixth to the ninth lunar months The gree of prematurity is not convincingly related to the size of e kidneys In infants with a crown rump length of 32 to 40 cm weight of the kidneys ranged from 40 to 575 gm while in

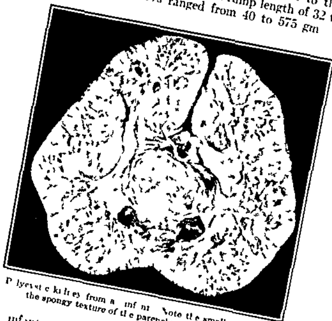


Fig 17 Polycystic kidney from an infant Note the small size of the cysts and the spongy texture of the parenchyma Photograph

full term infants the weight varied from 125 to 974 gm Presumably cystic kidneys continue to increase in size during intra uterine life but some enlarge much more rapidly than others The amount of functioning parenchyma is no greater in the small than in the large kidneys

On section the cortex seldom can be distinguished from the medulla and all parts of the organ are filled with cysts Often there is defective development of the pelvis and calices The most frequent microscopic appearance is a spongy tissue due to large numbers of small cysts (Figs 17 18)

Upon microscopic examination the persistent parenchyma when present is usually found chiefly in the subcapsular zone either in

the form of a continuous layer or more often as islands separated by cysts. Sometimes small clusters of tubules and glomeruli are found deeply placed between cysts, sometimes only scattered nephrons are found There is nearly always a great increase of loose or dense fibrous tissue between the tubules and cysts especially in the medullary portions, but the superficial part of the cortex under the capsule is often free from this connective tissue increase



Fig 15 —Polycystic kidney from an infant Note small cystic tubules. There is a great decrease in the number of nephrons Photomicrograph

Occasionally areas of cartilage or smooth muscle are found in the interstitial tissues (Busse, Berner) The significance of the excess

[illegible] is the marked reduction

[illegible] great many authors have noted this It has been estimated that the number may be reduced to 10 per cent of the normal but no actual counts have been made In the medulla there are only a few collecting tubules Normal convoluted tubules and glomeruli are commonly found only in

small islands usually in the subcapsular zone. Sometimes there are only rudimentary tubules and glomeruli between the cysts and no areas of normal cortex. Wakely found no tubules or glomeruli in 1 case.

The cysts are lined by a single layer of epithelium usually cubical but sometimes columnar or flattened. The cytoplasm is usually clear but sometimes granular. Intracystic papillary growths are not infrequent but the cysts are not filled with papillomatous growths as in the ovary.

In some kidneys numerous cysts show a glomerulus projecting into the lumen, the glomerulus being supplied with afferent and efferent arterioles and having a normal structure. In other kidneys no glomeruli can be found in the walls of the cysts. Beckman 1856 described glomerular cysts. Each cyst contains only one glomerulus. A cyst with a glomerulus in its wall is interpreted as a dilated capsular space. Other cysts are clearly dilated segments of a tubule since one frequently sees a normal glomerulus connected to a cyst by a normal tubular segment. Von Mutach 1895 studied a number of small cysts 0.5 to 2 mm in diameter in serial sections and was able to show that each was a dilated segment of a tubule. Good reconstructions were made by Meader 1907 and by Lorsman 1912 showing glomerular and tubular cysts. Lorsman stated that a cyst may be formed at any point in the course of the tubule. All investigators seem to agree that the cysts represent either dilated segments of tubules or dilated capsular spaces. There is also agreement that they very rarely communicate with the pelvis.

Hyaline glomeruli are almost invariably present in adult polycystic kidneys but they are rare in infants. None were found in our cases in infants but Stremmler noted a number in a stillborn infant.

The arteries and arterioles show a normal structure in all of our cases except 1 in which there is medial fibrosis causing the arterial walls to appear thicker and more homogeneous than normal. No intimal disease was observed.

Renal Function. Ten of our cases were stillborn and 12 lived less than 1 day. The remaining 6 lived from five days to fourteen weeks. No functional tests were made but it was noted that the infant that lived seventeen days had oliguria with albumin pus and blood in the urine. None had edema.

Several authors have described cases in infants with uremia. Kugelmass reported an infant two months old with convulsions, blood urea of 82 mg per cent and non protein nitrogen of 108 mg per cent. Tew studied a male infant six weeks old. The urine volume was reduced 50 per cent. Phenolsulphonephthalein output in two hours was 6 per cent and blood urea nitrogen 35.4 mg. The kidneys weighed 100 and 150 gm respectively.

In the cases in which some urine is formed it is clear that some tubules must communicate with the renal pelvis. Renal insuffi

ciency must be due to the great reduction in the number of nephrons that open into the pelvis. We cannot reconstruct clearly the structure of a cystic kidney in infancy which permits its possessor to survive into adult life and then die of uremia. No infant kidney has been described which is open to that interpretation but it is clear that those who survive must have much more normal parenchyma than is found in the infant kidneys that I have studied.

Associated Anomalies.—Other malformations are frequent in infants. Seven of the 28 infants in our series had other anomalies such as meningocele, anencephaly, encephalocele, club foot and bilateral hydrocele. Only 2 infants had cystic disease of the liver.

Unilateral Cystic Disease in Infants.—Six examples of unilateral cystic kidney in infants were found in our autopsies (Table 8). Four occurred in stillborn infants. The cystic kidney was larger than its normal mate except in No. 4. No. 5 was a male infant six months of age. The right cystic kidney weighed 73 gm., the left weighed 8.5 gm. and showed no cysts. The cystic kidney was not unlike the bilateral cases in structure except that it contained more normal parenchyma.

Cystic Kidneys in Childhood.—We have no examples of this group in our series. In the cases reported in the literature the clinical features are similar to those occurring in adults. There are no special features in most cases, but occasionally dwarfism results from the chronic renal insufficiency. Any anatomical type of renal disease in early childhood that brings about severe chronic renal insufficiency will cause dwarfism, the most frequent form being chronic glomerulonephritis. A case of renal dwarfism and rickets due to polycystic renal disease in a child ten years old was reported by Mazzeo. Cumming described an undersized girl fourteen years old who had had symptoms since the age of six years.

Bilateral Polycystic Disease in Adults.—These may be divided into clinical and subclinical groups.

Clinical Polycystic Kidneys.—The 70 cases of this group are listed in Table 9. The clinical symptoms have been discussed in previous pages but it may be helpful to give a few clinical histories to indicate variations in the course of the disease.

CASE 1 (Table 9). A woman aged twenty-seven years had noticed a mass in the left side for several years but it hadn't been painful. She had had two pregnancies and during each there was a marked edema of the ankles. Palpable left kidney. Three weeks before death no indigo carmine from either kidney in twenty minutes. Blood pressure 78/52. Symptoms and death from bacterial endocarditis. On section each kidney was filled with cysts but there were large areas of normal parenchyma between the cysts. This case illustrates the structure of the kidneys after some renal insufficiency has developed but before the stage of uremia.

CASE 27 (Table 9). A woman aged sixty-three years had an attack of hematuria with pain in the right flank one year before death. This was her first symptom. She was admitted to the hospital two weeks before

1550 gm and 1120 gm respectively The extremely cystic liver weighed 5370 gm This is the most frequent clinical type of the disease The absence of cardiac hypertrophy is noteworthy in view of the long history of hyper tension

Pathology —The kidneys are nearly all very large the combined weight of the smallest pair being 605 gm The combined weight was less than 1000 gm in only 7 of the 70 cases and the maximum was 6050 gm The smallest kidney weighed 260 gm and showed a fair amount of normal parenchyma Occasionally there is a marked difference in the size of the two kidneys (Nos 53 and 59 Table 9)

Microscopically the kidneys with few exceptions show only small islands of parenchyma between the cysts The areas of parenchyma show a zone of atrophy adjacent to the cysts indicating that the progressive expansion of the cysts gradually reduces the functioning parenchyma There are usually many hyaline glomeruli to be seen which with few exceptions seem to be due to atrophy of the associated tubules and not to vascular disease The arteries show only the changes corresponding to the age of the person The arterioles showed a moderate arteriolosclerosis in 4 of the 70 cases

Nos 71 72 and 73 (Table 9) deserve special consideration The cortices are filled with small cysts but the kidneys are small Microscopically there is extreme arteriosclerosis and arteriolosclerosis with hyalinization of nearly all the glomeruli The cysts play a minor role in producing the renal insufficiency These cases may be

fundamentally related to polycystic kidneys but the cause of uremia was vascular disease and not the cysts as in the other 70 cases Ritter and Baehr studied 3 cases in which they attributed uremia to vascular disease Cases of this type are probably accidental combinations of primary hypertension with moderate cystic disease There is no evidence that hypertension with moderate cystic disease is generally due to arteriolar disease as a few writers have maintained

Subclinical Polycystic Kidneys—In Table 10 there are shown 17 examples of polycystic disease found at postmortem in persons who died of conditions unrelated to the kidneys In none of these was the renal lesion suspected but presumably some evidences of its presence might have been elicited in the majority The kidneys are in general smaller than the clinical group the maximum combined weight being 1300 gm and only 2 pairs weighing over 1000 gm The most striking difference between the subclinical and clinical types is that the former have a relatively large amount of normal parenchyma between the cysts No functional tests were made but the anatomical evidence excludes renal insufficiency The blood pressure was elevated in 4 of the 8 cases in which it was determined Arteriosclerosis of moderate degree was present in only 1 case No 3

It appears highly probable that the subclinical group differs from the clinical type only in having fewer and smaller cysts Sieber thought that about one-eighth of the cases give no symptoms The absence of symptoms in some of the cases is due not so much to the size of the cysts as to their distribution When large areas of parenchyma are free of cysts as is sometimes the case it is unlikely that uremia would ever develop We may state therefore that i

Table 10 Subclinical Polycystic Renal Disease

Serial no	Autopsy no	Age	Sex	Blood pressure	Cyst size	Weight of heart gm	Weight of kidneys gm R	L
1	23 15[illegible]	[illegible]5	F	1[illegible]0 [illegible]	–	2[illegible]0	110	00
2	[illegible]3 750	C1	F	1[illegible]1 [illegible]3	+++	300	3[illegible]0	400
3	25-4[illegible]1	52	M	•	+	400	large	
4	26 9	45	F	•	+	3[illegible]5	325	52[illegible]
5	26-591	65	M	•	–	3[illegible]0	3[illegible]0	[illegible]00
6	2 2[illegible]	5[illegible]	F	•	++	235	[illegible]0	190
[illegible]	[illegible]0-53	33	F	1 [illegible]/10[illegible]	–	3[illegible]0	500	3[illegible]0
8	36 1[illegible]13	[illegible]5	F	110 [illegible]0	–	3 [illegible]	[illegible]7	14[illegible]
9	36 1 3	[illegible]	F		+	[illegible]5	1 5	12[illegible]
10	3 [illegible]9	61	M	14[illegible] 91	–	310	530	1[illegible]0
11	3[illegible] 1[illegible]9	60	M	[illegible]30 140	–	4 0	[illegible]00	600
12	39 [illegible]6	[illegible]3	M	1[illegible] [illegible]0	–	3	3[illegible]0	[illegible]0
13	39-4[illegible]0	54	F	164 11	–	3[illegible]0	4[illegible]	[illegible]0
14	41 1000	[illegible]	M		0	410	4[illegible]5	[illegible]
15	41 [illegible]04	[illegible]3	M		0	3 3	5[illegible]	[illegible]5
16	46-[illegible]3	[illegible]	M	1[illegible]3 10[illegible]	0	4 0	14[illegible]	14[illegible]
17	4[illegible] 101	84	M		0	4[illegible]5	2[illegible]0	2[illegible]0

subclinical group is composed in part of cases of a milder type with less involvement of the parenchyma that would probably never have progressed to uremia. It also contains kidneys which in time might have been largely destroyed by expansion of the cysts.

Unilateral Polycystic Disease (Table 8).—The incidence of the unilateral type has already been discussed. We shall now consider the special clinical and pathological features of our 8 cases in adults. In no instance was the lesion recognized clinically. Seven of the 8 cases died of some form of primary hypertension and 1 died of carcinoma of the stomach. The association with hypertension is presumably accidental since there was an associated arteriosclerosis of the kidneys in each of the seven cases.

In Nos. 7, 8, 9 and 10 the parenchyma was almost completely replaced by cysts; the kidneys were smaller but in other respects they did not differ from the bilateral clinical form. In two instances the cystic kidney was smaller than its normal mate. In Nos. 6 and 11, notwithstanding the large size, there was abundant normal parenchyma, and these kidneys resembled the subclinical type. There were no cases with cysts in the liver.

Associated Lesions.—Occasionally calculi are found in the pelvis and these may cause the clinician to overlook the underlying disease. Walters and Braasch found calculi in 5 of 85 cases, and Mazzeo found large bilateral calculi which contributed to renal insufficiency. In our case No. 43, Table 9, bilateral calculi were a contributory cause of death. In Washburn's case there was complete bilateral duplication of the pelves and ureters. Cystic disease of the liver was found in 30 of our 70 clinical cases, in 5 of the subclinical group, but in none of the unilateral group. Lejars found a cystic liver in 17 of 60 cases. There were no major anomalies in the adults such as are found in the infants.

Pathogenesis.—It has been established that the cysts in polycystic kidneys represent dilated segments of tubules or capsular spaces. The studies by von Mutach and the reconstructions made by Meader and by Lorsman show that any portion of the nephron may be dilated to form a cyst, and that cysts may communicate with normal segments of tubules. It is also clear that very few cysts open into the renal pelvis; such openings as occur may be due to secondary rupture. There is much evidence that many cysts are of the retention type, especially those that contain normal glomeruli in their walls. There is frequently hyperplasia of the epithelial lining of the cysts; papillomatous infoldings may develop (Melnikow). The hyperplastic changes may be interpreted as compensatory hypertrophy or as neoplastic in nature. To explain the origin of polycystic kidneys we must therefore take into account the following facts: (a) Numerous nephrons not connected with the pelvis which exhibit dilatation of any segment; (b) a great reduction in the total number of nephrons; (c) a progressive enlarge-

ment of the cysts (*d*) the hereditary nature of the disease and (*e*) the associated anomalies

In the normal organogenesis of the kidney the primitive ureter an outgrowth of the wolffian duct grows cranially and establishes contact with a formed mass of *mesodermal tissue called the meta* nephric blastema No tubules are formed in the metanephric blastema unless the ureteral bud makes contact with it The *primitive ureter expands at its distal end to form the renal pelvis* from which the calices develop as outpouchings From the calices a number of tubular buds are formed which grow into the meta nephric blastema These tubules divide and subdivide repeatedly to form the collecting tubules Each division of the collecting *tubules is referred to as a generation e g first generation second* generation and so on Each newly formed collecting tubule from the first generation onward comes into contact with the blastema which then forms a curved solid cap over its end The solid cap then forms a lumen and becomes the primitive convoluted tubule *The lumens of the two tubules then form a communication and* commonly the opposite end of the convoluted tubule develops a glomerulus Thus the original nephron is formed the collecting tubule arising from the ureteral bud the convoluted tubule from the *metanephric blastema*

having no outlet In the early embryonal period there are therefore normally numerous cysts in the kidneys formed from the first *few generations of tubules McKenna and Kampmeier have made* numerous reconstructions of these cysts Normally the fetal cysts atrophy but they might persist to form cysts

Ribbert 1900 offered the hypothesis that there is a failure of union between the newly formed collecting and convoluted tubules *and that the former then develop into cysts* But a fundamental objection to the failure of union theory is that the metanephric blastema does not de

a collecting tubule

any differentiation o

In u n lateral agenesis there

meta

bance

is indicated by the associated anomalies that are frequently present in the newborn group One may find anencephaly spina bifida encephalocele myelocele cranioracheschisis undescended testes

that polycystic kidneys are always congenital The strong hereditary influence also supports the view that a developmental disturbance is chiefly responsible and not an inflammation in the fetal kidney

An outstanding feature of the polycystic kidney is a marked reduction of the number of nephrons that make connections with the pelvis In the fetal type especially one finds only a few collecting tubules in the pyramids This may be explained as a failure of the original collecting tubules to divide as often as usual There is no satisfactory explanation of the cystic dilatation of the tubules

The progressive renal insufficiency observed in the adult type of the disease is clearly due to a slow increase in the size of the cysts with consequent atrophy of the adjacent parenchyma Hypertension is due to interference with the blood flow through the persistent parenchyma

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Solitary Cysts

Careful examination of the kidneys of adults at postmortem shows that over 50 per cent of them contain one or more small macroscopic cysts. No symptoms result from these cysts unless they become large and compress the kidney or adjacent viscera. In this discussion we are concerned only with large cysts (Fig. 19) the majority of which produce symptoms.

Although the large single cysts are referred to as "solitary," Hepler found 30 multiple and 9 bilateral among 249 reported cases.



Fig. 19. Solitary cyst of the upper pole of the kidney. Photograph.

One kidney may contain 2 or 3 large cysts or both kidneys may be affected (Cunningham). A solitary cyst in a single kidney was described by Graves. Commonly the cysts are unilocular but in a few instances they are broken up into small communicating chambers by fibrous septa (Maland and Brasch).

As regards gross features and content of the cyst cavity we may distinguish serous and hemorrhagic cysts. The former greatly outnumber the latter. Hepler surveyed 212 serous and 37 hemorrhagic

cysts The serous cysts are filled with a clear or cloudy fluid which has about the same urea content as the blood plasma and may contain traces of protein The lining is smooth and often an inner layer of cubical epithelium may be demonstrated The relatively thin wall is composed of fibrous tissue in which remnants of tubules may be seen The adjacent renal parenchyma is compressed by expansion of the cyst

Hemorrhagic cysts contain a reddish or chocolate colored fluid which owes its color to admixture with blood The rough inner wall is often covered with clotted blood, and there is no epithelial lining The fibrous walls are much thicker than those of the serous cysts Many of the hemorrhagic cysts contain tumor tissue—10 of the 37 surveyed by Hepler The authors usually consider the tumor a secondary formation in the cyst but these are in reality cystadenomas or

In one such case

were lined by th

masses of these cells in certain areas Stirling excluded those with tumors in his survey of hemorrhagic cysts

With respect to the relation of the cyst to the renal parenchyma

kidney is displaced to one corner of the sac like a testis in a hydro-

Most often the cyst contains 500 to 1000 cc of fluid but enormous cysts have been described which extended from the diaphragm to the pelvis Some contain as much as 10 liters of fluid (Krogius) In 1 of our cases an enormous cyst was adherent to the entire undersurface of the liver and extended to the pelvic cavity below

Most of the cases come to clinical attention between the ages of thirty and sixty years but a few occur in children The following

been reported Braun four months old, and

sies there were 38 examples of

Cysts of smaller dimensions

were very frequent but were not enumerated All of these cysts were asymptomatic the only one with clinical signs being the enormous cyst mentioned above

About two-thirds of the cases occur in females There is apparently a somewhat greater frequency on the right side The cyst may form at the upper pole the lower pole or the intermediate portion In 95 cases Harpster found 39 in the upper pole 20 in the

lower 6 in the convexity and 28 with position unstated. The symptoms vary somewhat with the position of the cyst.

Symptoms.—The most frequent symptom is pain in the region of the affected kidney which is usually in the form of attacks separated by intervals of varying length. The pain is sometimes accompanied by chills, fever, nausea or vomiting. Often a palpable tumor is found. Other frequent symptoms are dysuria, frequency and hematuria. Occasionally the initial complaint is a painless hematuria. The attacks may extend over a period of twenty years or more and usually they tend to recur at closer intervals as time goes on.

Cysts at the upper pole show special clinical features. In a survey of 32 upper pole cysts Quimby and Bright found that over half of the patients had pain in the upper quadrant under the costal margin. One-third had symptoms of cystitis and one-third had chills and fever. The tumor could be felt in only one-third of the cases. Seven patients had gross hematuria but two-thirds of them had normal urine. An accurate clinical diagnosis is difficult. Many cases are diagnosed cholecystitis. An abnormal pyelogram is usually found, the most constant changes being shortening of the calices and flattening of the pelvis adjacent to the cyst.

Cysts at the lower pole behave as retroperitoneal tumors causing displacement and compression of the intestines and gastrointestinal disturbances. They cause anterior and medial displacement of the ureter which may be seen in the urogram and they sometimes compress the ureter causing hydronephrosis and subsequent infection. Hofer described a case in which a large cyst compressed the common bile duct and brought on severe jaundice.

Upon cystoscopic examination blood or pus may sometimes be obtained from the ureter of the affected kidney or obstruction may be encountered in the passage of a ureteral catheter. Frequently the function of the affected kidney is depressed.

In a plain roentgenogram the enlarged kidney may often be visualized. In the event that the walls of the cyst contain calcium the cyst is readily outlined. The type of abnormality in the pyelogram varies with the position and size of the cyst. At the upper or lower pole the cyst often produces compression or distortion of the adjacent calices. Cysts in the mid portion produce elongation of the pelvis with distortion of the central calices. It may not be possible to distinguish cyst from hypernephroma and occasionally the pyelogram shows no abnormality. By means of a barium enema it may be possible to demonstrate anterior displacement and narrowing of the colon.

The treatment is entirely surgical. Partial nephrectomy is the operation of choice and is performed when any considerable part of the kidney can be saved but complete nephrectomy is usually necessary in the case of very large cysts. When adhesions of the cyst

wall to adjacent organs are present the technical difficulties of removal are increased

Nothing certain is known of the origin of solitary cysts They are presumably congenital Their infrequency in children may mean merely that enlargement begins in adult life There is no supporting evidence for the view that they develop in adult life from cystic dilation of tubules The hemorrhagic cysts are believed by many to originate as necrotic areas in the parenchyma (Hepler) but the evidence for this view is not convincing

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CHAPTER V

OBSTRUCTION OF THE URINARY TRACT—HYDRONEPHROSIS

HYDRONEPHROSIS may be defined as an overdistention of the renal pelvis with urine due to organic or functional obstruction in the urinary passages. We may speak of simple or non infected hydronephrosis when the fluid in the pelvis is clear and infected hydronephrosis when inflammation is present. The majority are infected. Pyonephrosis refers to the condition in which the pelvis is filled with pus; it is usually but not always dilated.

Normal Physiology of the Renal Pelvis.—Jona injected a radiopaque fluid into the renal pelvis under pressure low enough not to cause discomfort to the patient and then studied the contraction waves on a fluoroscopic screen. The calices were seen to contract in succession from above downwards, each contraction lasting one to three seconds with intervals of one to three seconds. The contraction wave begins at the attachment to the pyramid and passes toward the infundibulum. After the last calyx has contracted the pelvis empties its contents into the ureter. The globule in the ureter is spindle-shaped and is passed down the ureter by a peristaltic wave. The force which propels the urine into the bladder is furnished by the pelvic and ureteral musculature and not by the secretion pressure of the urine.

When the ureteral orifices are observed through the cystoscope the urine is seen to enter the bladder in spurts corresponding to the ureteral peristaltic waves, the intervals between the spurts decreasing as diuresis increases.

The bladder acts as a cushion to prevent undue pressure in the ureters and pelves. The ureteral sphincters prevent increase of intraureteral pressure when the bladder contracts.

The smooth muscle of the pelvis and ureter is supplied by motor sympathetic fibers. Stimulation of these nerves causes spasm of the musculature and denervation causes a moderate dilatation with suppression of peristalsis. Bilateral denervation in the dog, cat and rabbit causes uremia but unilateral denervation causes no permanent damage since peristaltic movements reappear after a few days. Evidently the musculature has autonomous activity. Splanchnic anesthesia in man stops ureteral peristalsis.

Pathological Physiology.—The first effect of a mechanical obstruction is increase of intraureteral and intrapelvic back pressure. Hinman found that when a mercury manometer is connected with a dog's ureter the pressure rises to 60 to 70 mm. Hg. It stays at this level for several hours and then falls gradually. After a few

weeks of obstruction the pressure is about 20 to 25 mm Hg and after a month it is less than 15 mm Hg There are intermittent variations in the level of the pressure In the obstructed ureter Morison noted peristaltic waves every 30 or 35 seconds

McDonald Mann and Priestly found a maximum pressure of 61 mm Hg in anesthetized dogs but in 12 unanesthetized dogs the maximum pressure ranged from 78 to 96 mm Hg These high pressures must be produced largely by the contraction of the ureteropelvic walls since they are higher than the glomerular capillary blood pressure The glomerular capillary blood pressure has been estimated at about 45 mm Hg It is higher than in other capillaries because of the closer relation to the arteries Landis found the blood pressure 32 mm Hg at the arterial end and 12 mm Hg at the venous end of capillaries in the skin

Wilmer measured the intrapelvic pressure in experimental hydronephrosis in the rabbit with a null point manometer and obtained much lower readings as follows third day, 7 5 sixth day, 27 5 *eleventh day 22 5 sixteenth day 23 5 twenty-eighth day 17 5* thirty-seventh day 20 and sixty-third day, 16 mm Hg These readings presumably represent the static pressure independent of increases produced by contraction of the pelvic musculature and they are consistent with the filtration pressure in the glomerular capillaries

Since the effective filtration pressure in the glomerular capillaries is the capillary blood pressure (45 mm Hg) less the colloid osmotic [illegible] mm Hg [illegible] Appar[illegible] [illegible]nephrotic kidney When experimental hydronephrosis is produced in the rabbit by ligature of one ureter injections of mercuric chloride or uranium nitrate do not injure the tubules of the hydronephrotic kidney It is believed that these poisons are filtered through the glomeruli and produce their injurious effects by being concentrated in the proximal convoluted tubules *The tubules of the hydronephrotic kidney* escape injury because glomerular filtration is largely suppressed Wilmer has shown that alkaline phosphatase disappears almost completely from the tubules after two or three days of complete ureteral obstruction This observation suggests disuse from lack of glomerular filtrate

In obstruction of the ureter the first notable change is dilatation of a segment immediately above the obstruction The dilatation then progresses upward to involve the pelvis In mild or early clinical cases only the ureters may be dilated With sudden complete obstruction dilatation is more prominent than hypertrophy but in chronic incomplete obstruction a marked hypertrophy may take place

In the early stages of hydronephrosis the pelvic fluid is not essen-

tially different from normal urine but it becomes progressively more dilute and finally contains only traces of urea and other substances Apparently the crystalloids diffuse out of the urine in the obstructed pelvis When an experimental hydronephrosis of about one week s duration is released and the kidney allowed to secrete it puts out at first a small amount of urine of low specific gravity but the renal function steadily improves Evidently complete urinary obstruction almost completely suppresses both glomerular and tubular functions A complete obstruction of over two weeks duration in the rabbit usually produces irreparable damage to the tubules

Pyelovenous Reflux —In 1924 Hinman and Lee-Brown demonstrated in retrograde pyelograms that the injected medium often passes from the pelvis into the kidney Under pressures as low

venous form seems to be much more frequent and more important than the other forms Pyelotubular backflow may be seen in the collecting tubules of the pyramids but the reflux probably does not extend beyond the medulla Fuchs believes that the medium first passes into the connective tissue about the calices (pyelointerstitial) and then breaks into the veins A reflux into the lymphatics has also been described

When a dye such as phenolsulphonephthalein is injected into the pelvis of a unilateral hydronephrosis it soon appears in the urine from the normal kidney

Since the pyelovenous reflux occurs at low pressures it is theoretically possible that in hydronephrosis with complete ureteral obstruction the kidney may continue to excrete some urine into the pelvis for a time the pelvic urine passing back into the renal veins In an infected hydronephrosis bacteria may be disseminated through the kidney in this way

Pathological Anatomy —The degree of atrophy in the kidney is of course much greater in unilateral than in bilateral hydronephrosis since in the bilateral form the patient dies of uremia before extensive atrophy can develop In persons dead of uremia from bilateral hydronephrosis there is commonly only moderate distention of the pelves and ureters but such kidneys have only a minimal functional capacity In a unilateral hydronephrosis of the same degree the kidney secretes only a small amount of urine of low specific gravity

Microscopic sections from the kidneys in bilateral hydronephrosis with uremia show no striking changes in the parenchyma There is only a moderate amount of tubular atrophy

Unilateral Hydronephrosis The late effects of hydronephrosis can be studied only in unilateral cases The distended ureter increases in length and becomes very tortuous The cortex becomes progressively thinner because of anemia from the increased pelvic

pressure and because of disuse atrophy of the tubules The pelvis increases in size as a result of the increased pressure and the atrophy of the parenchyma As the pelvis dilates the calices become wider shorter and more rounded until they are finally obliterated and the *pelvis becomes an ovoid sac with only shallow recesses corresponding* to the sites of the calices (Fig 20) After a few months the pelvis has usually attained its maximal size, and after this period its volume remains stationary or may even decrease In long standing unilateral hydronephrosis the distended pelvis is covered by a layer



Fig 20 —Severe unilateral hydronephrosis Note the marked distention of the pelvis and the extreme thinning of the cortex

... We have a number of ... nephrosis in which the ... g 30 to 50 gm and ex... the unilateral dwarfed kidneys may originate in this way Ligature of one ureter in the dog sometimes results in atrophy of the kidney In other cases the pelvis remains permanently very large and may contain as much as 500 cc of fluid

Microscopic Structure in Unilateral Hydronephrosis —The first

effect of obstruction is a moderate dilatation of some of the tubules but this soon gives way to a progressive atrophy The tubules become smaller as the individual cells decrease in size After a few months the cortex is greatly reduced in thickness and may have the appearance shown in Figure 21 which is characterized by intact glomeruli and small atrophic tubules The tubules are composed of small dark cells and they may exhibit lumina or appear as solid cords This stage of atrophy is never reached in bilateral hydronephrosis In some cases nearly all the tubules are atrophic but a few fairly normal nephrons (glomeruli and associated tubules) are seen

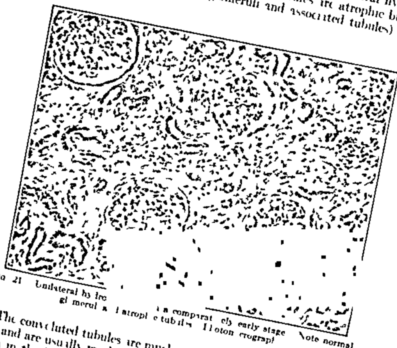


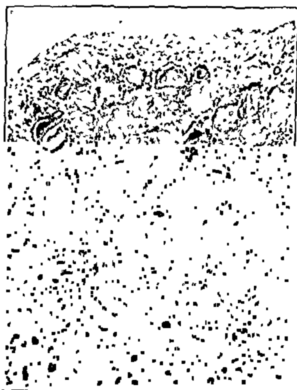
FIG 21 Unilateral hydronephrosis in comparatively early stage Note normal glomeruli and atrophic tubules Photomicrograph

The convoluted tubules are much more sensitive than the collecting and are usually markedly atrophic before any changes are to be seen in the latter There is little or no glomerular filtration and since the tubules have no work to do they undergo disuse atrophy In the course of months or years the glomeruli become hyaline They may persist as hyaline structures throughout life but often after many years they are removed by phagocytes The end result of unilateral hydronephrosis is usually a thin cortical layer composed of hyaline glomeruli and small collecting tubules filled with hyaline casts (Fig 22) Sometimes no glomeruli are to be seen but occasionally a few normal nephrons are still present

The tubular atrophy in hydronephrosis is probably due largely

to disuse, since glomerular filtration is suppressed, but the increased intrapelvic pressure may be a contributory cause in that it compresses the renal veins There is a marked reduction of renal blood flow in hydronephrosis but this may be an effect rather than a cause of the atrophy.

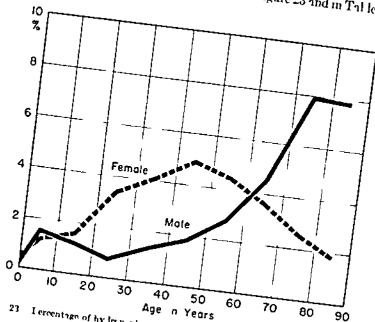
Hydronephrosis evidently produces a serious disturbance in the metabolism of the tubular epithelium since the alkaline phosphatase disappears almost completely after a few days of complete ureteral obstruction (Wilmer)



All
is of

Frequency —Hydronephrosis is the most common form of renal disease In our 59 064 postmortems there were 1825 cases of hydronephrosis an incidence of about 3 1 per cent This group does not include hydronephrosis from renal calculi, which is discussed in another chapter The high frequency of hydronephrosis is due to its causal relationship to so many forms of pelvic disease, *e g*, carcinoma of the prostate, bladder, uterus, ovary and rectum, hyper-

trophy of the prostate and uterine myomas. Except in a small group of cases of the congenital type hydronephrosis is always secondary to some other disease and is to be regarded in most instances as only a contributory or immediate cause of death. The actual number of cases studied is shown in Figure 23 and in Tables 11 and 12.



F 23 Percentage of hydronephros n a op es a e U ers y of Minnesota a c d g to age and sex

TABLE 11 D STR BUT ON OF HYDRONEPHROS S N MALES ACCORD NG TO AGE AND ET OLOGY

Age in years	Hyp ro h of p sta e	a noma of osta e	a noma f a	Oth o s ons of ladd	U ole ru on	F na u ole ruc ion	I re eral	I a al c a nal cor l	I ara congen tal	Tota
0-1	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
10-	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
0-40	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
40-[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
50-[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible] 0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible] 80	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible] +	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total	479	[illegible]	1	35	5	91	9	[illegible]	37	1 [illegible]35

Age and Sex There were 1235 males and 618 females with hydronephrosis in our autopsies an incidence of 3 3 per cent in males and 2 9 in females (Table 13) In Figure 23 it is shown that there is no great difference in the sexes until the age of twenty years In the age groups between twenty and sixty years *however hydronephrosis* is much more frequent in females chiefly because of the occurrence of pregnancy and uterine carcinoma during this period

TABLE 12 —DISTRIBUTION OF HYDRONEPHROSIS IN FEMALES ACCORDING TO AGE AND ETIOLOGY

Age in years	Carcinoma of uterus	Pregnancy	Carcinoma of bladder	*Other obstructions of bladder*	Urethral *obstruction*	External ureteral obstruction	Ureteral stricture	Paralytic spinal cord	Paralytic congenital	Total
Stillborn	0	0	0	0	0	0	2	6	0	8
0–10	0	0	0	2	1	2	12	16	6	39
10–20	0	3	0	3	0	4	2	0	1	13
20–30	9	33	*0*	*1*	*0*	7	2	2	*0*	*54*
30–40	33	21	0	1	3	10	8	3	0	79
40–50	60	5	6	2	0	33	5	4	0	115
50–60	5	0	8	6	1	33	8	7	1	[illegible]
60–70	41	0	9	7	1	35	9	3	1	106
70–80	16	0	13	4	0	[illegible]	9	0	0	64
80+	3	0	2	1	1	7	5	0	0	19
Total	219	62	38	[illegible]	[illegible]	153	6	41	9	618

TABLE 13 —PERCENTAGE OF CASES WITH HYDRONEPHROSIS ACCORDING TO AGE AND SEX

Age in Years	Males			Females		
	Total autopsies	Hydronephrosis	Percentage	Total autopsies	Hydronephrosis	Percentage
Stillborn	2495	8	0 3	2017	8	0 4
0–10	4 [illegible]	71	1 5	33[illegible]	39	1 2
10–20	*966*	12	*1 2*	*833*	13	1 6
20–30	1 [illegible]	13	0 7	1644	54	3 3
30–40	2[illegible]	3	1 3	1918	79	4 1
40–50	47[illegible]	86	1 8	2358	115	4 9
50–60	64 [illegible]	176	[illegible] 7	[illegible]	121	*4 4*
60–70	6674	301	4 5	[illegible]	106	3 6
70–80	4949	390	7 9	[illegible]	64	2 5
80+	1810	141	7 8	10[illegible]	11	1 8
Total	37 477	1235	3 3	21 [illegible]	618	2 9

but there is a great preponderance in males after the sixth decade chiefly because of prostatic disease A study of Figure 23 in connection with *Tables 11 and 12 will show that the age distribution is* dependent entirely upon that of the diseases which produce hydronephrosis

In the group under 10 years of age *the principal forms are those* due to stricture of the ureters or urethra and the paralytic types

There are relatively few cases between the ages of one and twenty years In the third decade the sharp increase in females is due largely to pregnancy In the fourth decade females greatly outnumber males because of pregnancy and carcinoma of the uterus The maximum frequency of hydronephrosis is attained in the fifth and sixth decades in females and in the eighth and ninth in males The great frequency of hydronephrosis in old men is due largely to hypertrophy and carcinoma of the prostate

Hydronephrosis in Stillborn Infants —There were 16 cases of hydronephrosis in stillborn infants due to lesions of the spinal cord (anencephaly spina bifida) congenital ectasia and ureteral stricture The hydronephrosis was often severe This is ample evidence that the fetal kidney excretes urine Wells demonstrated that ligature of the ureter in rats in utero results in hydronephrosis

A OBSTRUCTIVE HYDRONEPHROSIS

1 Urethral Stricture —Urethral stricture occurs almost exclusively in males

(a) In Children —In male infants congenital stenosis of the external meatus is seen occasionally often associated with phimosis There may also be obstruction of the fossa navicularis from redundant mucous membrane The lesion produces a narrow urinary stream or complete obstruction and is usually recognized by inspection An early meatotomy is indicated

Congenital valves in the prostatic urethra are an occasional cause of hydronephrosis in male children A mucous fold or a fibrous band arising from the verumontanum produces the stenosis According to Hinman about 100 cases have been reported in which the lesion was recognized through the cystoscope since Young made the first diagnosis in this way in 1912 There is usually a history of urinary difficulty since birth with slowness and smallness of the stream dribbling and sometimes incontinence and bed wetting There is a marked hydronephrosis with very large ureters Renal function is poor because of hydronephrosis and infection Pyuria is noted frequently The child is usually weak anemic and undernourished because of infection and renal insufficiency The diagnosis may be established by intravenous urograms when renal function is not too low Intraurethral urethrotomy is indicated to relieve the obstruction

In our [illegible] postmortems there were 13 cases of bilateral hydronephrosis in young children in which congenital obstruction of the urethra was demonstrated There were 6 males in which the obstruction was due to a valve-like membrane extending from the verumontanum The ages of these 6 children were as follows three weeks four months ten months eighteen months two years and two and a half years respectively Each child had severe hy-

lateral hydronephrosis with distension of the bladder. The oldest child had infection of the urinary tract.

There were 3 males, ages two hours, nine days and two years in which there was a marked stenosis of the membranous urethra. The oldest child had an imperforate anus which had been operated upon successfully.

A male sixteen months of age suffered from thirst, polyuria and diarrhea for thirteen months. At autopsy there was severe bilateral hydronephrosis with distension of the bladder due to generalized narrowing of the urethra.

Two males had atresia of the urethra in the glans penis and one female had complete atresia of the urethra. All three infants died within twenty four hours.

In addition to the 13 proven cases there were two other male infants in which obstruction of the urethra was highly probable but not conclusively established.

(*b*) *In Adults*.—In our records there are 33 cases of urethral stricture in males which caused hydronephrosis. One stricture was due to trauma to the perineum, another resulted from an operation and 31 were due to previous gonorrhea. In 1 instance the clinical signs of stricture first appeared at the age of seventy three years, fifty four years after the attack of acute gonorrhea.

There was one interesting case of congenital stenosis of the bulbo-membranous urethra. (Case Report A-47-1504) A male thirty-

six years

cent The

The blood

nually the

blood urea nitrogen was 130 mg per cent. At autopsy there was marked distension of the bladder, ureters and renal pelves. The cortices were thin. The right kidney weighed 90 gm, the left 68 gm. Microscopically there was marked tubular atrophy and chronic pyelonephritis.

The other 4 cases of urethral obstruction in males were due to neoplasms.

The 6 cases of urethral obstruction in adult females were due to carcinoma of the vulva (3), sarcoma of the vulva (1), carcinoma of the urethra (1) and surgical procedure (1).

The urethral strictures in males produced a severe hydronephrosis unless the stricture had been well dilated. The kidneys were usually infected. In every case death was due directly or indirectly to the stricture.

2 **Enlargement of the Prostate**.—(*a*) *Benign Hypertrophy*.—In our autopsies there are 470 instances of hydronephrosis due to

age (Table 11) Practically all cases of prostatic hypertrophy that progress to a fatal issue develop hydronephrosis but after prostatectomy or adequate drainage the hydronephrosis commonly recedes, although the infection may not subside. In 1 instance death from pyonephrosis resulted five years after prostatectomy. In about 0 per cent the hydronephrosis was unilateral and frequently one dney showed a greater degree of hydronephrosis than the other. Unilateral obstruction is due to uneven hypertrophy of the prostate with greater obstruction of one ureter. There were all degrees of hydronephrosis from slight to severe.

On the basis of the gross examination about 20 per cent showed no infection in the kidneys. The urine in the hydronephrotic sac was clear, the lining of the pelvis was smooth and no cortical abscesses were seen. On the other hand 80 per cent showed gross infection either in the pelvis or the cortex or in both situations. The urine was purulent, the pelvic mucosa was roughened or cortical abscesses were noted. Cortical abscesses were observed in 39 per cent. Cystitis was noted in nearly all cases with infected hydronephrosis. There is strong evidence of ascending infection of the kidneys in a great majority of the cases.

(b) *Carcinoma of the Prostate.* In our autopsies there were 218 cases of hydronephrosis due to carcinoma of the prostate. The age distribution shown in Table 11 corresponds roughly to that of benign hypertrophy. Thirty-three of the 218 cases were unilateral and approximately 70 per cent showed infection of the kidneys on gross examination. Cortical abscesses were frequent. Unilateral hydronephrosis is less often infected than a bilateral.

(c) *Other Forms of Prostate Enlargement.* There were 8 cases of bilateral hydronephrosis due to abscess of the prostate and 1 due to tuberculosis. Infection of the kidneys was present in 7 of the 9 cases. The men were younger than those with benign hypertrophy and carcinoma, the ages being twenty-eight, thirty-seven, thirty-nine, forty-one, fifty-six, fifty-seven, sixty-nine, seventy-three and eighty years respectively.

Prostatic hypertrophy from any cause produces distention of the bladder with residual urine. A patient with a large amount of residual urine tends to pass small amounts of urine at frequent intervals. The back pressure causes hydronephrosis which impairs the function of the kidneys. In about three-fourths of the cases the kidneys become infected with further damage to their function. There is decreased output of phenolsulphonephthalein, decreased ability to concentrate the urine and finally an elevation of the blood urea. Uremia is the usual cause of death. A great many patients have a definite renal insufficiency when they first consult a physician. Operative procedures are hazardous in the presence of marked renal insufficiency or severe infection. It has been found that gradual decompression of a distended bladder is unnecessary (Creevy).

It is the degree of renal insufficiency and the amount of infection that determine the outcome and not the rate at which the bladder is emptied. By establishing drainage of the bladder and treating the infection it is often possible to bring the blood urea back to normal before operation is undertaken, but sometimes the kidneys are so severely damaged that the blood urea continues to rise in spite of treatment.

3. **Obstructive Lesions of the Bladder.**—(*a*) *Carcinoma of the Bladder.*—In our group of 174 cases there were 136 males and 38 females. This tumor nearly always causes hydronephrosis, and it is more than twice as frequent in males as in females. It will be noted in table 12 that the average age is definitely less than that of the group with prostatic enlargement. Forty-two of the 174 cases were unilateral. Infection of the kidneys was present in 84 per cent, as determined by gross examination. There was no difference in the frequency of infection in unilateral and bilateral hydronephrosis.

(*b*) *Other Obstructive Lesions of the Bladder.*—In our records there are 39 cases of bilateral and 23 of unilateral hydronephrosis due to obstructive lesions of the bladder other than carcinoma. There are 6 papillomas, 1 melanoma, 1 myxoma, 1 sarcoma, 1 neurofibroma, 5 cases of tuberculosis, 7 of vesicular calculi, 31 of severe cystitis, 2 of diverticulitis, 2 of traumatic hemorrhage, 2 of abscesses under the trigone, 1 of uterine prolapse, and 1 of carcinoma of the vagina.

There was one case with obstruction of the neck of the bladder (No. 48-67). The patient, a male aged 27 years, had urinary symptoms since birth. At the age of 12 years he had marked distension of the entire urinary tract, with a blood urea of 56 mg. per cent and a blood pressure of 140/90 mm. Hg. Tissue was removed from the neck of the bladder through a suprapubic cystotomy.

He was much improved for several years. During the last week of life his blood pressure was 156/100 mm. Hg, and the blood urea nitrogen was 306 mg. per cent. At autopsy there was severe bilateral hydronephrosis and hydroureter with severe infection throughout the urinary tract. There was no demonstrable obstruction. The heart weighed 510 gm.

4. **Carcinoma of the Uterus.**—There were 219 cases of hydronephrosis due to carcinoma of the uterus, 206 of which originated in the cervix and 13 in the corpus uteri. The tumor grows out into the broad ligaments where it compresses the ureters. The age distribution is shown in Table 12. Sixty-two of the 219 cases were unilateral. Whether the hydronephrosis is unilateral or bilateral depends of course upon the manner of extension of the tumor into the broad ligaments.

Only 38 per cent of the 219 cases showed gross infection of the kidneys. Cortical abscesses were found in 21 of the 84 cases with infection. The kidneys are infected much less frequently from ureteral obstruction than from obstruction of the bladder or prostate.

5 Hydronephrosis Due to Ureteral Stricture There were 159 cases of hydronephrosis due to ureteral stricture about 8.5 per cent of all the hydronephroses. Forty cases were in infants under one year of age, but the rest were scattered through the various decades (Tables 11 and 12). There is no evident preponderance of either sex.

Uretero-Pelvic Obstruction. In our 159 cases of intrinsic ureteral obstruction (exclusive of calculi) there were 45 cases of uretero-pelvic stricture and 20 cases of obstruction at the uretero-pelvic junction associated with an artery to the lower pole of the kidney without a stricture.

(a) *Uretero-Pelvic Stricture.* Campbell stated that about one third of the ureteral strictures in children occur at the uretero-pelvic junction but only six of our 45 ureteral strictures in children under 10 years of age were in this situation. The ages of the 39 adults in the series ranged from nineteen to eighty five years. In all cases the stricture was unilateral, the renal pelvis was greatly distended and the ureter below the stricture was of normal caliber. In 8 instances the hydronephrotic sac was infected.

It appears highly probable that the great majority of these strictures are due to congenital narrowing of the ureter. Microscopic sections through the stricture show fibrosis of the ureteral wall but no inflammatory reaction. This may of course represent a healed inflammation but the frequent presence of ureteral stricture in children suggests a congenital origin. Many cases in adults have been reported in which symptoms had been present since childhood.

(b) *Uretero-Pelvic Obstruction Associated With an Accessory Renal Artery.*—In our group of 79 cases of unilateral hydronephrosis in adults limited to the renal pelvis there were 20 cases associated with an accessory artery to the lower pole of the kidney but without a demonstrable stricture (Fig. 21). Thus about one-third of the pelvic hydronephroses in adults seem to be due to an accessory artery and not to a stricture. The artery passes in front of the ureter and the pelvis overhangs it. With few exceptions the hydronephrosis was of the extrarenal type, i.e. the distended pelvis was chiefly outside the kidney as in Figure 21. The lumen of the ureter at the ureteropelvic junction is of normal caliber or only slightly narrowed. The degree of distension of the pelvis was moderate in 13 cases and severe in 7 cases. The pelvis was infected in 3 instances, and in one of these the resulting hydronephrosis was fatal. Only 4 of the 20 cases were diagnosed clinically. In one instance the distended pelvis contained over one liter of fluid and in another the hydronephrotic kidney was atrophic weighing only 15 gm.

The causal relationship of the accessory artery to hydronephrosis has been under discussion for nearly a century but is still not clearly understood. Hydronephrosis develops only in a small minority of the cases in which there is an accessory artery to the lower pole

9

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The causal relationship of the accessory artery to hydronephrosis has been under discussion for nearly a century but is still not clearly understood. Hydronephrosis develops only in a small minority of the cases in which there is an accessory artery to the lower pole

The percentage of cases with an artery to the lower pole cannot be determined from our records since the renal arteries are usually not described carefully but 55 cases have been found with this accessory artery but without hydronephrosis It is evident that some additional contributory factor must be present before the artery can produce hydronephrosis

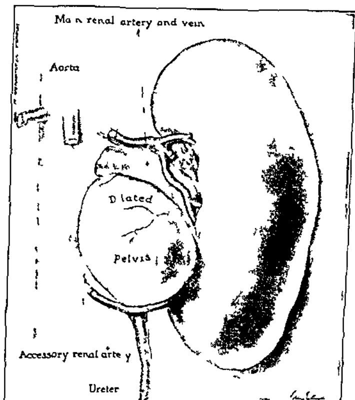


Fig 24 —Unilateral hydronephrosis with accessory renal artery Drawing

Many urologists report that accessory vessels are present in a large proportion of uretero-pelvic obstructions Jewett found accessory vessels to the lower pole in 30 of 70 cases The artery is nearly always anterior to the ureter but sometimes it is behind it (Dege)

There is a widespread opinion among urologists that the accessory vessel is the sole cause of the pelvic dilatation since the obstruction may often be relieved by section of the artery However Geraghty and Frontz found a uretero-pelvic stricture in addition to the artery Jewett saw 11 cases in which he regarded the accessory vessel as the sole cause of the obstruction and 8 cases in which a utero-pelvic stricture was present as well as the accessory artery

Jewett s 8 cases with stricture averaged thirteen years of age while those without stricture averaged twenty four years of age The symptoms in those without stricture were present nearly four times as long as in those with stricture

It has been suggested that there is a primary atony of the pelvis and that the artery has only an accidental relationship The observation that the hydronephrosis is usually extrarenal has lent some support to the view that it is different from the usual obstructive type but Jewett insists that extrarenal hydronephrosis also occurs in low ureteral obstruction and that it is dependent upon the original position of the pelvis outside the renal sinus and not upon the level of the obstruction Nevertheless an undue proportion of hydronephroses associated with the accessory artery are of the extrarenal type

The view that a movable kidney with an accessory artery tends to develop hydronephrosis has some support in the literature (Eisendrath) It is thought that the kidney sags downward producing a kink in the ureter In summary it may be said that in a majority of hydronephroses limited to the pelvis there is a definite ureteropelvic stricture and that a stricture is present in some cases in addition to an accessory artery to the lower pole but in many instances no stricture is present Increased mobility of the kidney is a possible factor in those without stricture

Uretero-vesical Stricture —Campbell found that about two thirds of the ureteral strictures in children occur at the lower end of the ureter In 44 of our 159 cases the stricture was situated in the wall of the bladder or at the ureteral orifice and 25 of the 44 cases were children under ten years of age Sixteen of the 44 cases were bilateral

The ureter may end blindly in the wall of the bladder or its lumen may be greatly narrowed as it passes through the bladder wall (Fig 25) Often the obstruction is caused by a membrane over the ureteral orifice Congenital atresia of the urinary orifice occurs in children and usually results in a ureterocele—a bulging of the dilated end of the ureter into the lumen of the bladder The ureterocele from one ureter may obstruct the other ureteral orifice and cause uremia (2 of our cases)

Zimmermann 1921 collected from the literature 70 cases of partial or complete closure of the distal end of the ureter in the bladder Twenty three cases showed incomplete closure Of the 47 cases with complete closure 5 showed obliteration of a segment of ureter in 37 the ureter ended blindly in the wall of the bladder and in 5 it ended blindly in some position about the bladder

There were 18 adults in our series with uretero-vesical stricture and in addition there was 1 instance of stricture of both ureteral orifices resulting from fulguration of a papilloma 1 from irradiation of a papilloma and 3 following prostatectomy The frequency of

these strictures in children lends support to the view that many of them in adults are of congenital origin

Strictures of the Body of the Ureter —Stricture may occur at any point along the course of the ureter In our group there were [illegible] strictures more than 1 cm distant from the extremities of the ureter They were more frequent in the upper and lower thirds than in the mid portion

There were 5 instances in infants of hydronephrosis due to a solid ureter and 2 due to multiple strictures In 8 instances the site of the stricture was not recorded

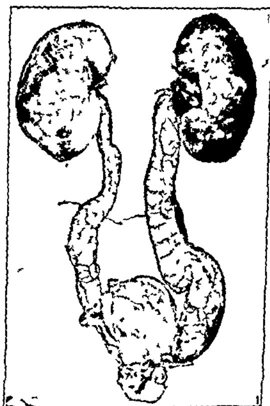


Fig. 9[illegible] Bilateral hydronephrosis in a child due to congenital ureterovesical strictures

Two cases of bilateral hydronephrosis in adults were due to accidental ligature of the ureters during hysterectomy and there were 3 unilateral occlusions due to primary carcinoma of the ureter

In 3 cases of extrophy of the bladder the ureters were transplanted into the sigmoid colon These patients developed bilateral infected hydronephroses

Symptoms and Diagnosis —In unilateral uninfected hydronephrosis in children with complete ureteral obstruction there is a large cystic retroperitoneal tumor of long duration In most instances of incomplete obstruction there are symptoms of persistent urinary infection the so-called chronic pyelitis of childhood There may be merely pain in the loin or there may be periodic attacks of severe pain with or without pyuria Gastrointestinal symptoms and fever are frequent Campbell Helmholz and others stress the importance of making urological studies in cases of chronic pyelitis that do not respond to medical therapy Intravenous urography will usually lead to the correct diagnosis

In adults there are often intermittent attacks of pain lasting from several hours to a few days with symptoms like those of renal colic There may be burning pain on urination with hematuria or pyuria Verhoogen and de Graeuwe reported 3 cases of long duration in adults A man aged forty eight years symptoms for eighteen years a boy aged sixteen years symptoms for fourteen years and a man aged thirty nine years symptoms for four years All 3 patients had long intervals in which they were free of symptoms The affected kidneys were found to be extensively destroyed

In adults the site of the stricture may be determined by ureteral catheterization and urograms

Treatment —The important consideration in treatment is the establishment of drainage Campbell states that strictures of the lower ureter can be successfully dilated but not those of the upper ureter Since the stricture tends to recur some urologists do an internal ureterotomy as a means of establishing better drainage After the obstruction has been relieved the infection usually responds to urinary antiseptics but it is difficult to get a sterile urine without good drainage Strictures of the upper ureter produce more damage to the kidney than those in the lower segment Frequently the kidney is so extensively destroyed that nephrectomy is necessary

In the case of hydronephrosis associated with an accessory artery to the lower pole the artery may be sectioned when not too large or a pyeloureteroplasty may be performed

6 **Hydronephrosis in Pregnancy** —By the use of intravenous pyelography it has been found that nearly 100 per cent of women show more or less ureteral dilatation during the third trimester of pregnancy The dilatation is in most instances limited to the ureters but the pelves are frequently involved The dilatation practically never involves the part of the ureter below the pelvic brim The right ureter is nearly always dilated in advanced pregnancy but the left ureter is affected in less than two-thirds of the cases The dilatation may begin as early as the eighth week and reaches its maximum in the sixth to eighth months It usually decreases somewhat during the last month Lewis and Baker in 49 pregnant women found dilatation on both sides in 26 cases and

on the right only in 20 cases There was none with dilatation limited to the left

The hydronephrosis of pregnancy is largely explainable on a mechanical basis i e pressure of the enlarged uterus upon the ureter at the pelvic brim The more frequent and more severe involvement on the right side is attributed to the fact that the uterus is directed somewhat to the right and rests its weight more on the right side The sigmoid colon intervenes to protect the left ureter to some extent The decrease of dilatation during the last month is attributed to the fact that the uterus assumes a more abdominal position at this period and does not exert so much pressure on the pelvic brim

Our 62 cases were selected because they had hydronephrosis and therefore do not give the frequency of hydronephrosis in pregnancy There were 9 cases in which death occurred during the first trimester *16 in the second and 37 in the third The degree of hydronephrosis* was usually greater in the more advanced stages of pregnancy It was bilateral in 31 cases limited to the right side in 27 and limited to the left side in 4 The hydronephrosis was slight when restricted to the left side Only 21 per cent showed infection in the kidneys The pyelitis of pregnancy is discussed under Pyelo-
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7 **Hydronephrosis From Miscellaneous Forms of External Ureteral Compression** There are 246 cases in our records of hydronephrosis due to miscellaneous forms of external ureteral compression the great majority of which are neoplasms The various lesions causing ureteral compression were carcinoma of the rectum or sigmoid 51 carcinoma of other parts of the colon 26 tumors and abscesses of the ovaries 53 tumors of the uterus (myoma) 19 uterine prolapse 2 metastatic tumors 36 retroperitoneal tumors 22 pelvic infections (abscesses) 16 and miscellaneous lesions 21 cases

One hundred twenty four of the 246 cases were unilateral and 122 were bilateral The degree of pelvic distention varied greatly and was often more pronounced on one side One or both kidneys were infected in 40 per cent

B HYDRONEPHROSES DUE TO NEUROMUSCULAR DISTURBANCES

In this form of hydronephrosis the increase of back pressure is not due to mechanical obstruction but to paralysis of the bladder or to functional disturbances in the ureter This group is often

referred to as paralytic or non-obstructive hydronephrosis We shall first consider the type in which there is a disease of the spinal cord sufficient to cause paralysis of the bladder

1 Paralytic Hydronephrosis Due to Disease of the Spinal Cord — The bladder receives parasympathetic fibers through the second third and fourth sacral nerves and sympathetic fibers through the presacral nerve The nerves contain both motor and sensory fibers which are relayed through the hypogastric plexus Stimulation of the sacral nerves causes contraction of the detrusor muscle with relaxation of the sphincter—the mechanism by which the bladder is emptied Motor stimuli through the presacral nerve seem to counteract the sacral motor fibers

Lesions of the spinal cord above the sacral level which disconnect the reflex center from the cerebrum cause a loss of voluntary control over urination The detrusor muscle is not stimulated to contraction hence the bladder becomes distended and finally transmits its increased pressure to the ureters and renal pelves Urination may be of the dribbling or overflow type or an automatic control may be established One of the most constant features of spinal cord disease is hydronephrosis resulting from paralysis of the bladder

During the prenatal period the emptying of the bladder is apparently controlled by the same reflex mechanism In anencephaly and spina bifida the infant is often born with hydronephrosis

In our autopsy records there are 5 cases of severe hydronephrosis in stillborn anencephalic female infants and 1 in a male infant that lived 16 hours Two stillborn females with rachischisis also had severe hydronephrosis

Spina bifida especially with meningocele or myelocele usually results in hydronephrosis In our series there are 6 stillborn infants 5 females and 1 male with severe spina bifida and hydronephrosis Another infant with a similar disease lived ten minutes There were 14 other children with spina bifida that died of uremia from hydronephrosis at the following ages three weeks two months three months (3 cases) four and a half months seven months eight months nine months fourteen months five years six years eight years and fifteen years In six of the older children the presence of a chronic renal infection was recognized clinically The child aged fourteen months and the boy aged fifteen years had spina bifida occulta

In spina bifida there appears to be a partial paralysis of the bladder which causes it to be more or less continuously distended The ureters are dilated and tortuous but they do not show the enormous hypertrophy characteristic of ureterovesical functional disturbances

Injuries of the Spinal Cord —There are 16 cases of hydronephrosis due to injury of the spinal cord The injury was a bullet wound

in 3 cases and fracture of a vertebra in 13 cases The duration of life after the injury was as follows four days seven days ten days eleven days sixteen days *nineteen days three weeks four weeks* five weeks five weeks eight weeks ten weeks four months nine months nine years and nine years respectively A mild degree of hydronephrosis without *infection was present in the person who* lived only four days Thirteen of the other 15 cases showed infection in the kidneys A fairly severe degree of hydronephrosis may develop within one week after severe *injury of the spinal cord The patient* who lived *nine months and the two who lived nine years after the* injury showed severe hydronephrosis with infection and in each death was due to *uremia The maximum blood pressures in the two* patients who survived nine years were 130 94 and 130 88 mm Hg

Syphilis of the Spinal Cord There were 27 cases of tabes and taboparesis and 15 *cases of other forms of neurosyphilis in which* moderate or severe hydronephrosis developed In tables the disturbance is due to *destruction of sensory fibers Thirty four of the* 42 cases of syphilis had infection of the upper urinary tract and about one half of them died of uremia

There were 13 cases of combined degeneration 8 of multiple sclerosis 13 of myelitis 7 *of* spinal cord tumors 1 of amyotrophic lateral sclerosis 1 of spinal abscess 1 of tuberculosis of the vertebrae and 1 of poliomyelitis in which hydronephrosis was a prominent feature at autopsy

Infection of the upper urinary tract was present in 39 of the 45 cases of this group and many of the patients developed uremia The hydronephrosis was always bilateral and seemed to be due to paralysis of the bladder

2 **Congenital Hydronephrosis** —In a small group of hydronephroses no obstruction can be demonstrated, there is no disease of the spinal cord and in most instances it seems to have been present since birth The etiology has not been established The bladder may be normal or it may participate in the paralysis Catheters are easily passed through the urethra and the ureters A characteristic feature of this group is the enormous hypertrophy and dilatation of the ureters The ureters are sometimes so large that they are confused with the intestines at postmortem The [illegible] present [illegible] to separate this group from [illegible] are several *types of* [illegible]

(*a*) *Stillborn Infants* [illegible] e 5 stillborn infants all males with severe hydronephrosis 3 of which were unilateral and 2 bilateral *The ureters were large and tortuous and were* more involved than the pelves One infant had polydactylism and another had partial cystic disease of one kidney The ureters were patent

(*b*) *Infants That Lived Less Than Forty-eight Hours* —There are

7 cases in this group the youngest eighteen minutes the oldest thirty-six hours One case was unilateral the others bilateral In 2 cases the hydronephrosis was limited to the ureters There were 2 cases of severe bilateral hydronephrosis with marked cortical atrophy one of which had an imperforate anus

(c) *Infants That Lived From Ten Days to One Year* —There are 10 cases in this group The ages at death were as follows Ten days five weeks eleven weeks fourteen weeks four months four and a half months five months eight months ten months and eleven months One infant fourteen weeks old died of congenital heart disease and showed a moderate bilateral hydronephrosis limited to the ureters The infant eleven months old had a unilateral hydronephrosis limited mainly to the ureter

Five infants had severe bilateral hydronephrosis with megaloureters and apparently died of uremia The three infants who died at ages five eight and ten months had clinical evidence of infection of the kidneys The hydronephrosis was bilateral and of moderate degree and the ureters were not very large The kidneys in each case showed severe infection

(d) *Well-defined Cases in Persons Over One Year of Age* These cases were studied clinically and are worthy of individual attention

CASE 1 —23-308 A baby boy aged one year developed an upper respiratory infection on April 30 followed by vomiting high fever convulsions pyuria and a gradual diminution of the urinary output The
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found in the cortices and the urine was purulent

CASE 2 A baby boy aged nineteen months Severe polydipsia and

and polycystic disease

CASE 3 36-2282 A male infant aged two years born normally at full term Control of the bladder was never established there had been continuous dribbling of urine since birth The mother noticed that the

nitrogen was 99 mg per cent An intravenous pyelogram showed practically no visualization of the left pelvis and marked dilatation of the right A cystogram showed a distended trabeculated bladder with reflux into a

large left ureter There was 550 cc of clear residual urine The blood pressure was 114/80 Hg

At autopsy there was found a severe bilateral hydronephrosis and hydroureter The ureters were very large There were numerous abscesses in the thin cortices and the urine in the pelves was purulent No obstruction was found in the ureters or the urethra

CASE 4 —46–2547 A female aged six years, had stones removed from each renal pelvis at the age of two and a half years, but she continued to have pyuria fever and anemia The blood pressure was not elevated The blood urea nitrogen ranged from 50 to 100 mg per cent At autopsy there was severe bilateral hydronephrosis with marked cortical atrophy and chronic pyelonephritis Both ureters were dilated and the bladder showed severe chronic cystitis No stones were found and there was no obstruction in the urinary tract

CASE 5 —19–138 A male child aged seven years, was taken ill suddenly on June 24 and died on July 8 from suppurative inflammation of the cavernous sinus His symptoms were referable entirely to this terminal illness, and there was no history of a urinary disturbance The urine contained a trace of albumin and a few leukocytes

At postmortem a marked bilateral hydronephrosis and hydro-ureter was found There was no infection in the urinary tract, and there was no obstruction in the ureters or urethra The ureters were enormously enlarged and thick walled

CASE 6 —36–524 A boy aged nine years, was admitted to the hospital on January 16 and died March 1 The record shows that at the age of six years he was troubled with enuresis and that he appeared anemic At the age of eight years he began to have attacks of pain in the region of the kidneys Upon admission the temperature was 99.2° and the blood pressure 156/120 mm Hg Only a trace of phenolsulphonephthalein was excreted in two hours, and the blood urea nitrogen was 121.3 mg per cent The hemoglobin ranged from 47 to 60 per cent

At autopsy there was severe bilateral hydronephrosis with marked cortical atrophy The ureters were enormous and their walls were thick There were abscesses in the cortices and the urine was purulent There was no obstruction in the ureters or urethra

CASE 7 —43–1937 A female aged ten years had had headaches and occasional projectile vomiting since the age of two or three years Examination about one week before death revealed hemoglobin, 11 gm, leukocytes, 28 450 albuminuria grade 3 blood urea nitrogen, 95 to 119 mg per cent, creatinine 6.9 mg per cent blood pressure 182/150 mm Hg, and hemorrhages and exudates in the eyegrounds At autopsy there was no subcutaneous edema but the peritoneal cavity contained 1000 cc of clear fluid The right kidney weighed 60 gm and the left kidney 30 gm Both kidneys showed marked hydronephrosis especially the left The ureters were two or three times normal size The bladder was normal There was no obstruction in the urinary tract Microscopically there is cortical atrophy with severe pyelonephritis

CASE 8 —40–718 A male aged eighteen years, developed a cold about three years before his death which was followed by acute glomerulonephritis He was confined to bed for eight months after which he seemed well until two weeks before death At this time he was found to have retinitis and a blood pressure of 202/140 mm Hg The blood urea nitrogen was 124 mg per cent At autopsy there was severe bilateral hydronephrosis and hydroureters There was no obstruction in the urinary tract Microscopically the kidneys showed advanced chronic glomerulonephritis superimposed upon congenital hydronephrosis

CASE 9 —23–685 A young man, aged eighteen years, was admitted to

the hospital on October 12 He stated that he had been well until October 1 when he had a sudden onset of abdominal cramps nausea and vomiting Since October 1 he had noticed polyuria and thirst He was well developed and well nourished There was a uremic odor to the breath and the blood urea nitrogen was 221 mg per cent The specific gravity of the urine was 1 010 and albumin + to +++ Death occurred on October 28

Autopsy revealed no edema but a serofibrinous pericarditis There was a very marked hydronephrosis with megalo-ureters but there was no infection in the urinary tract There was no obstruction in the ureters or the urethra

Case 10 —19-3 A male, aged seventeen years had been troubled with dribbling of urine since infancy He had always been weak and pale and his growth was stunted his height being only 124 cm There was no particular change in his condition until November 19 1918 when he began to have attacks of nausea and vomiting Since December 19 1918 he had had several attacks of marked dyspnea There was pyuria and constant dribbling of urine The bladder was distended Death January 8 1919

At autopsy there was no edema There was severe bilateral hydronephrosis *more* marked on the left The renal cortices were very thin and there was an abscess in the right lower pole The ureters were very large and the urine was purulent There was no obstruction in the ureters or the urethra The bladder was distended and trabeculated

Case 11 45-2265 A male aged 21 years Several attacks of uremia during the last few years At autopsy there was severe bilateral hydronephrosis with massive enlargement of the kidneys and ureters The bladder was distended There was no obstruction in the urinary tract Microscopically there was severe cortical atrophy without infection There was no record of the blood pressure but the heart weighed 425 gm

Case 12 —A male aged 34 years Symptoms for only 6 weeks Headache Nausea Hemoglobin 54 per cent Blood pressure 198 100 mm Hg Blood urea nitrogen 150 mg per cent The left kidney and ureter were absent There was severe hydronephrosis and hydroureter of the right with purulent urine There was no obstruction

Case 13 —34 930 A male aged thirty-seven years was admitted to the hospital May 15 1934 complaining of dyspnea and swelling of the ankles The edema disappeared at night The onset of his illness was about five years ago at which time he had severe headaches and was told by his physician that he had nephritis Intermittent spells of headache continued from that time Five months before admission he had an attack of dyspnea with edema of the ankles and another similar attack occurred about March 1 1934 The last attack was associated with hematuria

Upon admission May 15 1934 the temperature was 97 2° and the blood pressure 240 140 mm Hg The heart was enlarged to the left and there was pitting edema of both legs The urine had a specific gravity of 1 007 and albumin +++ The blood urea nitrogen was 56 mg per cent on May 17 and 73 mg on the day of death May 26

At autopsy the heart showed left ventricular hypertrophy and weighed 530 grams The right kidney weighed 60 and the left 100 grams Both kidneys showed extreme hydronephrosis with marked cortical atrophy of the patchy coarse type There was a double ureter on the left Both ureters were dilated but their walls were thin There was no obstruction in the ureters The bladder was distended and its walls were thin There was no urethral obstruction Gross examination of the spinal cord showed no disease

Microscopically the kidneys show severe pyelonephritis with lymphocytic infiltrations in the medullary and deep cortical portions which have produced areas of atrophy corresponding to the deep cortical depressions There

are only scattered islands of persistent glomeruli and tubules. The arteries and arterioles all show very thick walls and narrow lumina brought about by atrophy and medial fibrosis. The changes in the arterial vessels are clearly due to disuse atrophy. A large majority of the glomeruli are hyaline but in the islands of persistent parenchyma open glomeruli are found.

This case appears to be a primary hydronephrosis of the congenital paralytic type with a superimposed chronic pyelonephritis. The hypertension is presumably due to the renal lesion and the cardiac hypertrophy is attributable to the long standing hypertension.

There has been a great deal of discussion of the etiology of non-obstructive hydronephrosis. There are some who maintain that this group merely represents cases in which an obstructive lesion was overlooked but many competent observers have reported cases in which they could not find an obstruction. The most widely accepted explanation is a lack of coordination between ureteral peristalsis and relaxation of the ureterovesical sphincter. It is believed that the sphincter does not relax when the peristaltic w[ave] reaches it. This failure of the sphincter to relax is called achal[asia]. The megalo-esophagus which occurs with cardiospasm, the hy[per]trophied stomach in infants with pylorospasm and the megaloco[lon] of Hirschsprung's disease are regarded as due to achalasia of [the] respective sphincters. Hepler cites cases from the literature [in] which non-obstructive hydronephrosis has been found in associatio[n] with megalocolon and also with megalo-esophagus. Occasionall[y] more than one sphincter shows achalasia.

There is however some difficulty in accepting achalasia of the sphincters as the complete explanation of the hydronephrosis since as Foerstnerdt pointed out, the ureteral openings are widely patent and show no movements of opening or closing. At postmortem they are certainly widely patent and clinically ureteral catheters are easily introduced. One gets the impression that the primary disturbance is paralysis of the ureterovesical sphincters and that the back flow during contraction of the bladder is responsible for ureteral dilatation and hypertrophy. Normally the ureters are protected from increased pressure during contraction of the bladder by the ureteral sphincters but if these are relaxed the ureters really become a part of the bladder and are subjected to a distention to which they are not adapted.

In most instances the ureteral walls are greatly hypertrophied but occasionally they are distended and thin. In many cases the bladder participates in the paralytic process since it is constantly distended and may be of the "overflow" type with continuous dribbling of urine.

It may be said in conclusion that the evidence points rather to paralysis of the ureterovesical sphincter than to achalasia as the primary disturbance.

The Blood Pressure in Hydronephrosis.—The blood pressure was recorded in 1031 cases of hydronephrosis. Blood pressures taken

TABLE 14.—SYSTOLIC BLOOD PRESSURES IN HYDRONEPHROSIS ARRANGED WITH RESPECT TO THE AGES OF THE INDIVIDUALS

	Bilateral hydronephrosis				Unilateral hydronephrosis			
	Below 150 mm Hg		150 mm Hg or higher		Below 150 mm Hg		150 mm Hg or higher	
Age in years	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Below 50	93	71	38	29	49	73.1	18	26.9
Above 50	323	50.4	318	49.6	94	49.0	98	51.0

shortly before death after the onset of vasomotor collapse were not tabulated. In Table 14 the systolic pressures are arranged with respect to age and in the bilateral and unilateral forms. It will be noted that age is a very important influence, hypertension being nearly twice as frequent in those over fifty years of age as in those under that age. There is no significant difference in the incidence of hypertension in the unilateral and bilateral forms of hydronephrosis.

Wetherby recorded the blood pressures of 1558 dispensary patients over fifty years of age. Perhaps there were more with hypertension than would be found in a normal population but only a small percentage had symptoms referable to high blood pressure. Thirty-eight per cent of the men and 57.5 per cent of the women had a systolic pressure of 150 mm Hg or higher. In our series about 50 per cent of those over fifty years of age had hypertension but our group includes a larger proportion of very old men than Wetherby's because of the large number of cases of prostatic disease. It appears that when all forms of hydronephrosis are considered together there is no demonstrable influence of hydronephrosis on blood pressure. Hypertension appears to be related to the age of the individual rather than to the hydronephrosis.

No correlation could be established between the degree of hydronephrosis and the level of the blood pressure. That renal insufficiency does not play an important role is indicated by the close correspondence of the uni- and bilateral forms.

However, as will be shown presently, certain forms of hydronephrosis do cause hypertension.

A detailed study of hypertension in hydronephrosis in the various decades was made.

1st Decade. There is only one case in this decade, a boy aged nine years with congenital hydronephrosis and a blood pressure of 150/120 mm Hg. See Case 6, page 138.

2nd Decade. There are 5 cases in this decade.

(a) A female aged ten years with congenital hydronephrosis and a blood pressure of 182/150 mm Hg. See Case 7, page 138.

(b) 40 1005. A female aged eleven years with congenital extrophy of the bladder. Bilateral uretero-sigmoidostomy during first year of life. Repeated febrile attacks. Hypertension first noted at age of eight years. Terminally the blood pressure was 180/100 mm

Hg and the non protein nitrogen 78 mg per cent At autopsy the left kidney was completely destroyed by hydronephrosis and infection It weighed 15 gm The right kidney had a double pelvis with two ureters in the sigmoid The lower half showed hydronephrosis and abscesses

(c) 47-825 A male aged fifteen years born with imperforate anus Anoplasty The urine passed through the rectum until the age of five years when the fistula was closed During the last year of life there was a gradual rise of blood pressure and of blood urea The terminal blood pressure was 166 126 mm Hg and the blood urea nitrogen 236 mg per cent At autopsy there was severe bilateral hydronephrosis with chronic pyelonephritis

(d) A male aged eighteen years with congenital hydronephrosis and chronic glomerulonephritis Blood pressure 202 140 mm Hg See Case 8 page 138

(e) 46-1642 A female aged nineteen years Renal symptoms since early childhood Anemia Blood pressure 188 120 mm Hg Blood urea nitrogen 135 to 210 mg per cent The left kidney weighed 550 gm There was severe distension of the pelvis and ureter The cortex was very thin There was no ureteral opening in the bladder The right kidney was hypoplastic weighing 60 gm Microscopically it showed chronic glomerulonephritis

3rd Decade —There are 7 cases in this decade

(a) A male aged twenty years Left kidney removed three years before death because of an injury Blood pressure 188 144 mm Hg Blood urea nitrogen 132 mg per cent Severe hydronephrosis of right kidney ureter normal Microscopic examination shows chronic glomerulonephritis

(b) 45-2265 A male aged twenty-one years Congenital hydronephrosis See Case 11 page 139

(c) 40 1520 A male, aged twenty two years Mesonephric ridge carcinoma with severe left hydronephrosis and hydroureter Blood pressure 150 105 mm Hg Microscopic sections show atrophy and chronic pyelonephritis Since the heart weighed only 250 gm the interpretation is acute hypertension

(d) 40-1561 A female aged twenty six years Eight months pregnant Blood pressure 182 100 mm Hg Moderate right hydronephrosis Eclampsia

(e) 44 82 A female aged twenty-six years Carcinoma of the cervix Blood pressure 150 100 mm Hg Severe bilateral hydronephrosis and hydroureter Microscopic sections show pyelonephritis Heart 280 gm Diagnosis acute hypertension from hydronephrosis

(f) 48 67 A male aged twenty-seven years Congenital obstruction of the neck of the bladder Blood pressure 150 100 mm Hg See 48-67 page 128

(g) A male aged twenty-eight years Never strong as a child

Symptoms for 18 months before death dyspnea fatigue edema of ankles Blood pressure 180 120 mm Hg Blood urea nitrogen 175 mg per cent Heart 380 gm A single kidney at the pelvic brim showing severe hydronephrosis No obstruction Microscopic sections show chronic glomerul nephritis

4th Decade —There are nine cases with hypertension in this decade

(*a*) A male aged thirty two years with multiple sclerosis Blood pressure 170 80 mm Hg Bilateral hydronephrosis No microscopic study

(*b*) Unilateral hydronephrosis in a male thirty two years old from carcinoma of the testis Blood pressure 154 118 mm Hg no renal arteriolosclerosis

(*c*) A male aged thirty four years Congenital hydronephrosis of a single kidney Blood pressure 198 100 mm Hg *See* Case 12 page 13[illegible]

(*d*) A [illegible] re 180 100 mm Hg ([illegible] osis Heart [illegible] per tension [illegible] ervix

(*e*) Severe bilateral hydronephrosis from carcinoma [illegible] in a woman thirty eight years old Blood pressure 175 100 mm Hg No microscopic study

(*f g h*) Three cases of eclampsia with moderate hydronephrosis

(*i*) Congenital hydronephrosis in a male aged thirty-seven years Blood pressure 240 140 mm Hg *See* Case 13 page 139

5th Decade —There are 12 cases in this group with a systolic blood pressure of 180 mm Hg or higher and a diastolic above 90 mm Hg in which tissue was available for microscopic study Nine of the kidneys showed arteriolosclerosis and one showed chronic glomerulonephritis

Persons Over 50 Years Old In the group with a systolic pressure of 180 mm Hg or higher there were 118 cases in which the kidneys were available for microscopic study Arteriolosclerosis was present [illegible] Grade 1 31 cases Grades 2 and 3 50 [illegible] in incidence [illegible] n [illegible] 150 [illegible] p but

and 150 mm Hg No evi[illegible] random sampling indicates that arteriolosclerosis is [illegible] In the litera

Hydronephrosis as a Cause of Acute Hypertension [illegible] reports of moderate hypertension from [illegible] oma of the [illegible] follows [illegible] rate by [illegible] rty two [illegible] pressure [illegible] laterally

170 80 male aged thirty t[illegible]

dronephrosis blood pressure 154/118; female aged thirty-eight years carcinoma of the cervix uteri bilateral hydronephrosis blood pressure 175/100. It has been observed that the blood pressure may return to normal after urinary drainage has been established. None of the cases of this type has been followed very long and it has therefore not been established that chronic hypertension would result.

It has often been noted in men with prostatic hypertrophy and hydronephrosis that the blood pressure falls after catheterization but a similar fall of pressure usually occurs when the patient is put to bed without catheterization.

By ligature of the urethra temporary hypertension may be produced in a rabbit but permanent hypertension has not been produced in animals by experimental hydronephrosis.

Levy, Mason and Harrison produced acute hypertension in 3 of 8 dogs by ligature of the ureter. They found a marked reduction of renal blood flow in acute hydronephrosis. There are several clinical reports in which it is claimed that hypertension disappeared after removal of a hydronephrotic kidney. It is maintained that hydronephrosis produces renal ischemia which results in hypertension as in the Goldblatt experiment, but the reduced renal blood flow may be the result of a decreased demand for blood by the non-functioning kidney and not the result of vascular obstruction.

It may be concluded that hypertension of severe degree often develops in long standing cases of hydronephrosis of the congenital type and that transitory hypertension sometimes occurs in other forms of hydronephrosis but in the great majority of hydronephroses with chronic hypertension the elevated blood pressure is due usually to an associated primary hypertension rarely to chronic glomerulonephritis.

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CHAPTER VI

GLOMERULONEPHRITIS

In a broad sense *glomerulonephritis* includes all renal diseases in which there is a primary injury ... sense it refers to obstructive l... which are severe enough to ... renal function

... of primary

B Exudative glomerulonephritis—glomerular abscesses
C Hemorrhagic glomerulonephritis without capillary obstruction
D Focal glomerulonephritis
(a) Thrombotic
(b) Proliferative
E Membranous glomerulonephritis—lipoid nephrosis

The clinician may prefer to think of acute nephritis as a disease of sharp onset with symptoms referable to renal dysfunction but such a concept has little value to the pathologist since this syn... ...ular and inter... ...ll therefore

... is by far the most frequent form of clinical glomerular disease and its symptoms are referable to obstruction of the glomerular capillary circulation The obstruction of the capillaries is usually caused by increase in the number and size of the capillary endothelial cells but sometimes the glomerulus is compressed by a large epithelial crescent The acute type must be distinguished from subacute and chronic forms since only the acute stage may terminate in complete recovery

In the literature the various anatomical types of acute nephritis are seldom clearly distinguished and for this reason it is difficult to compare the observations of previous investigators with our own ... hemorrhagic nephritis is negligible ...ute pro... ...leath in a high percentage

The death ratios of the different forms of glomerulonephritis are arranged with respect to age and sex in Table 15 This is of course not the clinical incidence of the disease since about one-half of the

acute cases recover completely but it may be seen that about 1 per cent of deaths in persons over one year of age are due to glomerulonephritis and that there is no significant difference in the sex incidence

TABLE 15 — DEATH RATIOS OF THE DIFFERENT FORMS OF GLOMERULONEPHRITIS IN THE VARIOUS DECADES

	Males No of Cases				Females No of Cases			
Age Years	Total Autopsies	Acute	Subacute and Chronic	Lipoid Nephrosis	Total Autopsies	Acute	Subacute and Chronic	Lipoid Nephrosis
0–10	4733	7	8	16	3377	5	2	7
10–20	966	3	19	1	843	5	18	7
20–30	1761	2	53	4	1644	4	26	4
30–40	2882	7	36	9	1918	4	23	4
40–50	4725	2	35	7	2358	2	18	1
50–60	6476	6	24	6	2842	0	13	1
60–70	6674	5	18	3	2073	5	2	2
70–80	4949	3	6	2	2560	0	4	1
80–105	1916	0	1	0	1059	0	1	0
Totals	34982	35	200	48	19570	5	107	27
		0 10%	0 57%	0 18%		0 13%	0 55%	0 14%

It will be noted in Table 15 that the deaths from acute glomerulonephritis are distributed rather irregularly through the different decades with no preponderance in young persons as one might expect The ages varied from one to seventy two years (Table 16)

In the case of chronic glomerulonephritis the maximum incidence and highest death ratios are in the second third and fourth decades There is evidence that the average duration of life after the acute attack in the chronic form is about ten years It may therefore, be inferred that acute glomerulonephritis occurs most frequently in the first and second decades

Seegal Seegal and Lyttle analyzed the clinical records of 381 cases of acute glomerulonephritis from several hospitals, the diagnoses being made from the hospital records without separation of the different types They found that about 50 per cent of the cases

and Rastetter found the maximum incidence in the second decade

Our data do not of course give the clinical frequency of acute glomerulonephritis

Sex — Seegal Seegal and Lyttle found acute glomerulonephritis about twice as frequent in males as in females Murphy and Rastetter reported 102 males and 48 females Our data show no

cases of this type have been divided into two groups Group I,

CHAPTER VI

GLOMERULONEPHRITIS

In a broad sense glomerulonephritis includes all renal diseases in which there is a primary injury to the glomeruli in a more restricted sense it refers to obstructive lesions of the glomerular capillaries which are severe enough to produce important disturbances of renal function

Histologically we may distinguish the following types of primary glomerular disease

A [illegible]

B Exudative glomerulonephritis—glomerular abscesses

C Hemorrhagic glomerulonephritis without capillary obstruction

D Focal glomerulonephritis
   (a) Thrombotic
   (b) Proliferative

E Membranous glomerulonephritis—lipoid nephrosis

The clinician may prefer to think of acute nephritis as a disease of sharp onset with symptoms referable to renal dysfunction but such a concept has little value to the pathologist since this syndrome may be produced by glomerular tubular vascular and interstitial lesions as well as by extrarenal factors We shall therefore [illegible] r the [illegible] toms are referable to obstruction of the glomerular capillary circulation The obstruction of the capillaries is usually caused by increase in *the number and size of the capillary endothelial cells* but sometimes the glomerulus is compressed by a large epithelial crescent The acute type must be distinguished from subacute and chronic forms since only the acute stage may terminate in complete recovery

In the literature the various anatomical types of acute nephritis are seldom clearly distinguished and for this reason it is difficult to compare the observations of *previous investigators with our own* The mortality from acute benign hemorrhagic nephritis is negligible yet very few investigators distinguish this type from the acute proliferative form which terminates in chronic nephritis or death in a high percentage

The death ratios of the different forms of glomerulonephritis are arranged with respect to age and sex in Table 15 This is *of course* not the clinical incidence of the disease since about one-half of the

acute cases recover completely but it may be seen that about 1 per cent of deaths in persons over one year of age are due to glomerulonephritis and that there is no significant difference in the sex incidence

TABLE 15 DEATH RATIOS OF THE DIFFERENT FORMS OF GLOMERULONEPHRITIS IN THE VARIOUS DECADES

	Males No of Cases				Females No of Cases			
Age Years	Total Autopsies	Acute	Subacute and Chronic	Lipoid Nephrosis	Total Autopsies	Acute	Subacute and Chronic	Lipoid Nephrosis
0–10	4733	7	8	16	3377	5	[illegible]	7
10–20	966	3	19	1	833	5	18	7
20–30	1761	2	53	4	1644	4	26	4
30–40	2882	7	36	9	1918	4	23	4
40–50	47[illegible]5	[illegible]	3[illegible]	7	2358	2	18	1
50–60	6476	6	[illegible]4	6	[illegible]842	0	13	1
60–70	[illegible]674	5	18	3	297[illegible]	5	2	2
70–80	4949	3	6	2	2560	0	4	1
80–105	1816	0	1	0	1059	0	1	0
Totals	3498	35	[illegible]00	48	195[illegible]0	[illegible]5	107	27
		0 10%	0 57%	0 18%		0 13%	0 55%	0 14%

It will be noted in Table 15 that the deaths from acute glomerulo nephritis are distributed rather irregularly through the different decades with no preponderance in young persons as one might expect The ages varied from one to seventy-two years (Table 16)

In the case of chronic glomerulonephritis the maximum incidence and highest death ratios are in the second third and fourth decades There is evidence that the average duration of life after the acute attack in the chronic form is about ten years It may therefore be inferred that acute glomerulonephritis occurs most frequently in the first and second decades

Seegal Seegal and Lyttle analyzed the clinical records of 381 cases of acute glomerulonephritis from several hospitals the diagnoses being made from the hospital records without separation of the different types They found that about 50 per cent of the cases occurred in the first decade about 20 per cent in the second 15 per cent in the third and small percentages in subsequent decades Hayman and Martin in 77 clinical cases found 6 in the first decade 22 in the second 23 in the third and 26 after the third Murphy and Rastetter found the maximum incidence in the second decade

Our data do not of course give the clinical frequency of acute glomerulonephritis

Sex —Seegal Seegal and Lyttle found acute glomerulonephritis about twice as frequent in males as in females Murphy and Rastetter reported 102 males and 48 females Our data show no significant difference in the death ratios for males and females but we are dealing with a relatively small group

GROUP I —**Acute Diffuse Proliferative Glomerulonephritis** —The cases of this type have been divided into two groups Group I,

TABLE 16.—ACUTE PROLIFERATIVE GLOMERULONEPHRITIS OF PRIMARY TYPE

Serial No	Autopsy No	Age	Sex	Duration of symptoms	Albuminuria	Hematuria	Edema	Blood pressure mm Hg	Renal function	Weight of kidneys gm	Etiology	Comment
1	36-602	1	M	5 wk	4	0	0	?	?	200	Pharyngitis otitis media	Sp grav 1 024
2	24 540	2	M	1 wk	?	?	1	110/?	?	250	Scarlet fever (3 wk)	Anuria, crescents 3
3	42 2200	3	M	Few wk	2	1	1	?	?	145	Impetigo	Symptoms 1 wk after impetigo marked edema of lungs, crescents 4
4	28 1109	5	F	6 da.	3	1	2	?	?	139	None	Severe oliguria, sp. grav 1 030 passive congest. of liver
5	33 288	5	M	8 da	+	0	0	?	UN 169	300	Sore throat primary peritonitis	Onset with sore throat capillary thrombi
6	43 1500	6	F	5 da	?	?	1	[illegible]/60	UN 60	275	Tonsillitis (3 wk)	Ascites, 1000 cc tonsillitis
7	45-977	6½	M	3 da	4	2	1	150 100	—	198	Lobar pneumonia	
8	29-553	7	F	4 da	?	?	3	?	?	150	Scarlet fever (? wk)	Strep. viridans bacteremia
9	37 1642	7	F	6 da	?	?	1	?	?	148	Sore throat (3 wk)	Death from edema of lungs
10	37 1706	7	M	3 da	4	0	1	?	?	150	Impetigo (3 wk)	Death from edema of lungs
11	33 469	7	M	?	?	1	0	?	?	?	Scarlet fever (6 wk)	Death from edema of lungs
12	40 1141	9	F	3 wk	2	1	2	128 98	UN 120	390	Sore throat	Severe oliguria, venous pressure 18 cm water
13	23 33	11	F	1 wk	3	1	2	?	?	230	None	
14	13 140	12	F	3 mo	3	0	4	?	?	Normal	Pneumonia	Pn peritonitis
15	19 152	12	M	5 wk	3	0	2	132 94	?	245	Smallpox	
16	44 370	13	F	3 mo	0	—	0		—	440	Primary peritonitis	
17	33 1398	14	F	9 da	?	?	1	—100 115	?	170	Sore throat bronchitis	
18	36 377	15	M	3 wk	4	1	0	168 110	UN 24 (? wk)	310	Scarlet fever	Strep bacteremia sp. grav 1 022
19	23-419	16	F	3 wk	2	0	0	154 92	UN 36 (3 da.)	295	3 wk after labor	Sp grav 1 026
20	40 1668	16	M	2 mo	?	1	0	150 80	?	300	Otitis media (3 mo) meningitis	
21	40 1303	20	F	10 da.	4	1	1	108 69	UN 247	475	Puerperal endometritis	
22	40-206	20	F	17 da.	?	1	1	1 8 52	SP grav 1032	330	Lobar pneumonia	Oliguria 5 da. Ascites 2000 cc Spleen 4 0 gm Empyema
23	43 589	25	M	11 da.	2	2	1	?	NPN 71 6 da.)	530	Infected hand (3 wk)	Infection of hand oliguria severe edema of lungs
24	19-62	27	M	5 wk	3	0	1	?	?	290 (1)	Infected wound	Infection after nephrectomy crescents 4 cap thromboses
25	37 190	27	F	3 wk	3	0	1	189 132	?	300	Acute pericarditis	Thrombosis of arterioles and capillaries, wire loop lesions crescents 2
26	44 1655	28	F	2 mo.	2	1	0	112 73	UN 57	410	Otitis media (? mos.)	Plasma proteins 6 3 gm crescents 4
[illegible]	45-62	31	F	1 mo.	—	0	1	—195 130	UN 24	273	Puerperal endometritis	

TABLE 16.—ACUTE PROLIFERATIVE GLOMERULONEPHRITIS OF PRIMARY TYPE
(*Continued*)

Serial no	Autopsy no	Age	Sex	Duration of symptoms	Albuminuria	Hematuria	Edema	Blood pressure mm Hg gm	Renal function	Weight of kidneys gm	Etiology	Comment
28	34 1434	32	M	2 mo	3	0	3	180/110	NPN 140	535	Cold cough (2 mos)	Onset 1 wk after a cold hgb 23% crescents 4
29	32 1432	32	M	5 wk	3	0	3	180/110	NPN 159 (5 da.)	535	Bronchitis (9 wk)	Sp grav 1 020
30	36-99	32	M	2 wk.	4	1	0	158/90 204/120	UN 100 8	708	Sore throat (2 wk	Strep bacteriemia
31	15-230	34	M	?	?	?	0	?	?	490	?	
32	35-638	35	M	2 wk	4	0	3	146/90	UN 35 (1 hr)	460	None	Death from edema of lungs sp grav 1 017
33	35 793	35	F	6 wk	2	?	2	?	UN 70	?	None	Death from edema of lungs
34	22-468	35	M	2 mo	?	1	2	100/?	?	365	Pneumonia empyema	Thick basement membranes
35	23 208	36	F	2 mo	2	0	1	190 124	?	460	Sore throat	Sp. grav 1.020
36	39 876	37	M	25 da	4	1	1	180/110	UN 182	548	Laryngitis	Oliguria sp grav 1.012 to 1.020 total protein 3 6% gm
37	35-1181	38	F	3 wk.	?	?	0	90/50	?	394	Pneumonia	
38	24 288	40	F	1 mo	2	0	1	180/110	UN 32 (3 wk)	490	None	Sp grav 1 011 cap thromboses
39	35 752	44	F	10 wk	4	0	2	150/60	UN 56 (2 wk)	970	None	Ruptured aneurysm
40	30 507	44	M	7 wk	2	0	1	162/100	UN 205	424	A cold	
41	48 754	48	M	3 wk	2	0	0	248 140	—	330	A cold	Primary hypertension
42	21 108	51	M	1 mo	?	?	2	228/110	?	630	None	
43	33-302	51	M	16 da.	3	0	3	164/80	?	420	Sore throat (3 wk)	
44	21 108	51	M	1 mo	+4	1	3	190/100	?	630	None	
45	15 165	55	M	6 wk	2	1	2	?	?	Normal	None	
46	45 1510	55	M	3 wk	2	0	0	—	—	550	Cellulitis	Severe infection of neck
47	29 253	58	M	10 da	4	1	3	130/68	UN 75 (2 da)	6 0	Influenza (3 wk)	Sp grav 1 015
48	26 19	60	M	?	?	?	0	?	?	330	None	
49	28 189	61	M	6 wk	3	1	0	150/75	UN 145 (3 wk)	370	Sore throat	Cap thromb
50	30-576	61	M	3 wk	3	0	0	?	?	550	Sore throat (1 wk)	Oliguria anuria
51	45-1507	61	F	6 wk	4	0	1	155 90 230 110	UN 45	300	Sore throat	Chiefly exudative type
52	29-1799	62	M	1 mo	4	0	1	190/105	UN 190 (8 da)	550	Influenza (1 wk)	
53	17 176	66	F	1 mo	3	0	1	?	UN 72 (2 wk)	300	A cold bronchitis	Thromboses of arterioles cap thrombi
54	40 2336	66	F	?	1	0	2	?	?	190	?	
55	40 1911	67	F	?	?	?	0	140/54	?	3.2	Bacteriemia	
56	30 919	68	F	1 mo	?	?	0	190/90	?	385	A cold (3 mo)	Crescents 1
57	46-773	68	M	1 mo	1—	1	0	100/56	UN 16	255	—	Onset with fever chills cough Huntington's chorea
58	41 381	71	M	2 wk	2	0	0	—	—	255	Cellulitis of arm	Chiefly exudative type
59	38-774	72	M	?	?	?	2	160/120	?	450	?	
60	44-407	72	M	3 wk	4	1	1	158 90	?	410	None	Venous pressure 14 5 cm H_2O no passive congestion of liver crescents 4

UN, blood urea nitrogen NPN non protein nitrogen The time before death when the nitrogen determination was made is indicated

TABLE 17 — ACUTE PROLIFERATIVE GLOMERULONEPHRITIS COMPLICATING ANOTHER DISEASE

Serial no	Autopsy no	Age	Sex	Duration of symptoms	Albuminuria	Microscopic hematuria	Edema	Blood pressure	Renal function	Weight of kidneys gm	Major disease	Comment
1	37-910	11	F	3 wk	1	1–	0	?	?	210	Lupus erythematosus	
2	32-619	13	M	3 wk	2	1–	1	190/74	UN 78 (4 da.)	400	Pulmonary tuberculosis	Began with a "cold" severe lesion
3	36-714	14	F	2 mo +	2	1	0	104/?	NPN 262	530	Bacterial endocarditis	
4	39-2723	16	F	?	2	1–	0	104/56	?	494	*Cooley's anemia, septicemia*	
5	39-2266	17	F	?	3	1–	0	?	PSP 0	350	Bacterial endocarditis	Capillary thromboses oliguria
6	29-581	19	F	6 wk	?	?	2	170/?	?	350	Puerperal endometritis	Strep viridans bacteremia
7	17-202	25	M	?	3	?	4	140/80	?	515	Bacterial endocarditis	
8	48-2993	26	M	7 wk	3	1	3	165/105	UN 19	470	Cirrhosis of liver	Serum proteins 3.8 gm per cent
9	18-122	30	M	?	3	1–	3	?	?	530	Bacterial endocarditis	
10	37-198	33	M	3 wk	4	1	2	210/147	NPN 125	570	Primary hypertension	Heart 550 gm
11	31-1473	37	M	?	3	1–	2	190/70	UN 30 (3 mo.)	275	Aortic valve defect	
12	*36-71*	*40*	*F*	*?*	*3*	*1*	*1*	*137/78*	*UN 86 (6 da.)*	*341*	*Unresolved pneumonia*	*Capillary thrombosis*
13	33-618	44	M	?	3	2	3	168/68	UN 39 (2 wk.)	550	Bacterial endocarditis	No embolic lesions, Strep viridans
14	41-675	44	F	?	?	?	0	110/64	?	395	Bacterial endocarditis	Crescents 4 diffuse embolic lesions
15	37-931	46	M	3 mo	2	1	0	130/68	NPN 231	450	Bacterial endocarditis	
16	35-630	48	M	6 da.	4	1	3	170/115	?	495	Lobar pneumonia	Moderate
17	44-176	49	M	3 wk		—	1	168/88 230/40	—	330	Bacterial endocarditis	
18	20-270	55	M	?	?	?	3	?	?	397	Primary hypertension	
19	32-391	56	F	?	2	1–	1	160/90	UN 77 (1 da.)	315	Primary hypertension hydronephrosis	
20	*35-504*	*57*	*M*	*?*	*3*	*1–*	*0*	*187/89*	*UN 194*	*695*	*Primary hypertension acute rheumatic endocarditis*	
21	16-43	59	M	3 wk	?	?	1	140/?	?	573	Diabetic gangrene	
22	32-782	60	M	?	2	1–	1	265/142	UN 34 (1 mo.)	450	Primary hypertension	Capillary thrombosis
23	40-2258	60	M	1 mo +	4	1	1	180/90	UN 113	473	Primary hypertension	Partly exudative
24	32-798	62	M	3 mo.	1	1–	1	220/140	UN 103 (1 da.)	610	Primary hypertension	
25	32-255	62	M	?	?	?	0	200/100	?	441	Primary hypertension	Capillary thrombosis
26	34-2142	64	F	3 wk.	2	1–	0	150/94	UN 76	350	Parkinson's disease	
27	39-986	66	M	?	?	?	2	178/88	?	475	Primary hypertension	Heart 650 gm.
28	41-954	67	F	?	3	1	2	170/110	UN 149	395	Primary hypertension	Severe acute proliferative
29	23-360	69	M	10 da.	4	1–	1	?	?	370	Primary hypertension	Began with a "cold"
30	33-64	74	M	?	1	1–	3	190/75	?	310	Pyonephrosis	
31	46-1791	76	M	10 wk.	1	0	2	1?6/78	UN 87	446	Primary hypertension	
32	30-239	78	M	?	?	1	2	130/78	UN 138	700	Infected surgical wound	
33	29-436	78	M	3 wk.	?	?	2	215/110	UN 131	260	Primary hypertension	
34	37-1651	Adult	M	?	?	?	0	170/90	?	505	Bacterial endocarditis	

UN blood urea nitrogen NPN non protein nitrogen The time before death when the nitrogen determination was made is indicated

Table 16 includes the cases in which nephritis was the major illness and the direct cause of death Group II Table 17 includes the cases in which the nephritis was a terminal complication of another disease Group I is more satisfactory for clinical study since the symptoms are not overshadowed by those of the major illness

Duration of Symptoms —The duration of the disease is presumably somewhat longer than the duration of the symptoms The

to four weeks 11 one to two months 17 two to three months 8 unknown duration 6 (Table 16) The shortest duration was three days By definition cases of more than three months duration were classified as subacute or chronic

In those that lived less than one week death was usually due largely to edema of the lungs or larynx In those that lived over one week uremia was the usual cause of death but occasionally pneumonia peritonitis or bacteriemia were important contributory factors The cases in which death was not due to uremia give opportunity for the study of the earlier stages of the disease

The Urine —There is usually a moderate decrease in the amount of urine and in severe cases a marked oliguria or even anuria may develop The specific gravity of the urine is commonly normal in mild cases and in the early stages of severe forms but with the onset of uremia a more dilute urine is excreted The specific gravity in our fatal cases ranged from 1 011 to 1 032 the majority being above 1 020 However even in the presence of uremia the specific gravity is seldom as low as in chronic glomerulonephritis with insufficiency

Albuminuria —Albuminuria is a constant finding in acute glomerulonephritis The absence of albuminuria excludes this diagnosis The outstanding feature of the disease is injury of the glomerular capillaries which invariably results in leakage of protein through

proliferation Completely obstructed glomeruli do not transmit any protein and the maximum leakage of protein occurs in lipoid nephrosis with no capillary obstruction The amount of protein in samples of urine varies with the diuresis and usually a fairly

although albuminuria decreases as healing proceeds In general a *marked albuminuria* indicates nephritis of some form but Murphy and Rastetter found no relation between the degree of albuminuria and the subsequent course of acute glomerulonephritis Albuminuria obviously is related to glomerular and not to tubular injury

Hematuria —Gross hematuria refers to the condition in which *there is sufficient blood in the urine to give it a reddish tinge* Murphy and Rastetter found gross hematuria in 32 per cent of 150 clinical cases but only 2 of our 60 cases of the acute proliferative type showed gross hematuria However, the urine is always bloody in benign hemorrhagic nephritis

In centrifuged samples of urine erythrocytes are practically always found but the number of red cells is often not impressive In only 22 of our 47 cases in which the sediment was examined was there any considerable number of erythrocytes (Table 16) Examination of the sediment is however not an accurate method for determining the number of erythrocytes one should do an Addis count In normal urine one may find a few erythrocytes [illegible] renal [illegible] ision [illegible] nt to establish [illegible]

The erythrocytes escape from open glomerular capillaries not from those closed by endothelial cells In microscopic sections one *sees that the erythrocytes have escaped from capillaries that appear* normal The fact that red cells escape from a capillary is evidence that it is not permanently damaged Hematuria in itself is not a grave feature in glomerular disease In clinical experience glomerular lesions with gross hematuria but without edema hyper*tension or renal insufficiency* offer a good prognosis (page 164)

Edema The degree of edema (subcutaneous edema ascites hydrothorax) is roughly indicated in Table 16 by numerals Since the degree varies from time to time the *average condition is indicated* It will be noted that edema was absent at all times in one- [illegible] ere only 19 cases in which [illegible] and Rastetter observed [illegible] was never a severe com*plication in their experience However in 5 of our cases edema of* the lungs was the immediate cause of death Severe edema of the lungs may develop when there is little or no subcutaneous edema (Nos 9 10 11) *The presence of edema is not necessary to* establish the diagnosis of any type of acute nephritis except lipoid nephrosis

The factors that determine the development and the intensity of edema in acute glomerulonephritis are not well understood The *depletion of the plasma proteins is probably* the most important factor in some instances but some observers have found the pro-

teins only slightly reduced at the height of the edema The proteins were determined in only 2 of our cases In No 36 the total protein was 3 62 gm with a Grade 1 edema, and in No 26 with no edema the total protein was 6 3 gm

Several writers have noted acute dilatation of the heart with decompensation in acute glomerulonephritis (Franke, Levy Murphy *et al*, Masters *et al*) This has been noted especially in patients with marked hypertension and is demonstrable in roentgenograms In 3 of 27 fatal cases Murphy and his associates attributed death to heart failure, and in 15 of their 24 cases myocardial insufficiency of varying degrees was noted An increase of venous pressure is frequently observed and passive congestion of the liver is occasionally seen at postmortem LaDue, in a study of 12 cases of acute glomerulonephritis with edema, found increased venous pressure and cardiac dilatation in every instance

In No 4, with Grade 2 edema, there was chronic passive congestion of the liver and in No 12 with Grade 2 edema the venous pressure was 18 cm of water In No 60, with Grade 1 edema, the venous pressure was 14 5 cm of water but there was no passive congestion of the liver It is therefore probable that increased venous pressure from cardiac decompensation is often a contributory or a major cause of the edema

A few authors attribute edema to widespread capillary injury with increased permeability (Page, Rennie) This view seems to be based upon the conception that the edema fluid in nephritis has a relatively high protein content like an inflammatory exudate, and that it is not a transudate But Fahr and Kerkhof found the protein content of edema fluid in acute nephritis very low as it is in cardiac edema, when they were very careful in obtaining edema fluid free from contamination with blood There is no longer any

acterized by hemorrhages, not by edema

Since there is usually oliguria in severe acute glomerulonephritis, it is possible that this is a contributory cause of edema especially when the fluid intake is increased in an effort to increase the output of urine In 1 of our cases a fatal pulmonary edema was caused by this treatment However, one may see anuria without edema, No 50

It appears probable that edema is related to lowered colloid osmotic pressure, increased venous pressure and retention of fluid, but more detailed investigations must be made before the relative

60
it

[illegible]

erulonephritis there being only 13 cases with a pressure of 180 mm Hg or higher The low blood pressure of Nos 34 and 37 probably represent a terminal vasomotor collapse The patient may develop uremia with a normal blood pressure but this does not occur frequently Murphy and co-workers found hypertension in 74 of 94 patients It is generally agreed that hypertension may be absent at all times in acute glomerulonephritis *and that in mild* cases it is often found only during the first few days A very high pressure is an unfavorable prognostic sign and no case can be regarded as healed if hypertension is still present Persistent hypertension beyond the acute stage indicates the development of chronic nephritis However *an occasional patient with severe hypertension* recovers completely

Cerebral Symptom [illegible] pecially in children there may [illegible] the brain viz severe headach [illegible] of vision *transient palsies and coma These symptoms are most apt to* occur when the blood pressure is high They are usually due to uremia but sometimes they occur in the absence of renal insufficiency and in this type of case the symptoms are probably caused by increased intracranial pressure from an excess of subarachnoid fluid since the spinal *fluid* is under increased pressure and removal of fluid often brings relief Papilledema (choked disk) occurs occasionally and is also referable to increased intracranial pressure

Renal Insufficiency —In mild cases that terminate in recovery there is usually little or no elevation of blood urea but cases occur in which there is a sharp rise of *blood* urea after several days probably because of oliguria which is followed by a rapid decline after diuresis becomes normal A very high blood urea is an unfavorable feature but recovery may still take place A progressive increase of blood urea is a very unfavorable prognostic sign

In the early stages of cases that terminate *fatally* there is usually only a moderate nitrogen retention and death may result from *edema of the lungs bacteriemia or peritonitis* before the onset of uremia (Table 16) The level of blood urea nitrogen shown in Table 16 is closely related to the time before death when the determination was made the high readings were usually obtained shortly before death

The phenol sulphonephthalein excretion measures *the immediate* functional capacity of the kidneys and has no great prognostic value *since the renal function* may improve or deteriorate rapidly The measurement of blood urea is more informative since it represents a cumulative effect of renal insufficiency

The functional disturbance is due to obstruction of the glomerular capillaries with decrease of glomerular filtration

Etiology —Our observations agree with those of nearly all others that there is usually a history of some infection preceding acute glomerulonephritis By far the most common antecedent infections are those of the upper respiratory tract such as tonsillitis bronchitis and common colds A large variety of other infectious processes occasionally precede the nephritis such as smallpox chickenpox infected wound pneumonia and impetigo contagiosa In most instances the antecedent infection produces a lesion of a mucous membrane which allows the entrance of bacteria into the tissues

Volhard and Fahr 1914 obtained a history of upper respiratory infection in 125 of 179 cases The following summary is quoted from Hayman and Martin who collected 976 cases from the literature

Antecedent infection	Per cent
Sore throat tonsillitis	32 1
Upper respiratory infections	24 4
Otitis and sinusitis	5 7
Scarlet fever	6 4
Skin infections	4 1
Pneumonia	4 0
Rheumatic fever	1 7
Miscellaneous	10 3
No known infection	11 3

In our 60 cases there were 3 in which no clinical history was obtained and there were 11 cases without clinical evidence of a preceding infection In the remaining 46 cases there was a history of scarlet fever in 4 sore throat and other upper respiratory infections in 18 otitis media in 2 a cold in 4 infected wound in 2 puerperal sepsis in 3 pneumonia in 5 impetigo contagiosa in 2 cellulitis in 2 peritonitis in 1 smallpox in 1 bacteriemia in 1 and pericarditis in 1 case

Judged by the antecedent infections proliferative glomerulonephritis is usually caused by streptococci Hemolytic streptococci are probably more often the causative agent than non hemolytic

from the blood

capillary walls. When bacteria lodge in the glomerular capillaries they produce focal lesions and not diffuse endothelial proliferation.

Several investigators have suggested that the glomeruli must first be sensitized to a particular bacterial protein before the corresponding organism can produce the lesion, and there are several arguments in favor of this hypothesis. (*a*) The interval between the attack of scarlet fever and the onset of glomerulonephritis is usually two or three weeks. (*b*) A person with chronic glomerulonephritis is highly susceptible to streptococcic infections and commonly develops an exacerbation with each attack of pharyngitis. (*c*) The fact that glomerulonephritis is a rare complication of streptococcic infections is evidence that a simple invasion of the blood stream by streptococci rarely produces the glomerular lesions. (*d*) Fahr and Masugi have produced glomerulonephritis in the rabbit by the injection of anti-rabbit-kidney duck serum. An emulsion of rabbit kidney is injected into a duck and serum from the duck is then injected into a rabbit. The nephritis obtained is characterized by large numbers of epithelial crescents with little or no endothelial proliferation. The best results are obtained when the duck serum is injected directly into the renal artery of the rabbit. The reaction thus resembles the Arthus phenomenon. Masugi believes that the antibody for rabbit kidney in the duck serum reacts with the rabbit kidney to produce the lesion, but Kay has shown that the process is more complicated and is related to the formation of antibodies for duck serum in the injected rabbit.

There is, however, no convincing evidence that bacterial allergy is concerned in the origin of glomerulonephritis. No investigator has succeeded in producing glomerulonephritis in animals by previous sensitization with bacterial proteins. There is usually an interval between an infection and the onset of nephritis, but this may be less than one week, which is hardly sufficient time for the development of sensitization. *Streptococcic infections are so common* that one would expect a much higher incidence of glomerulo-

[illegible]

but we know that the [illegible]
and non hemolytic types.

Group II. Acute Proliferative Glomerulonephritis Complicating [illegible] 31 examples [illegible] death [illegible] minal [illegible] much [illegible] the [illegible] tions [illegible] ptoms

Because of the major illness the duration of the [illegible] ptoms cannot be determined accurately. *The glomerular lesions do not* differ in any important respect from those of Group I. Often the

major illness was of infectious nature and may be regarded as the direct cause of the nephritis. This is particularly true in bacterial endocarditis of which there are 9 examples. In a majority of cases of bacterial endocarditis there is a subclinical glomerulonephritis (Bell 1936) and these 9 cases merely represent more extreme degrees of this process. There are 9 other cases in which the major illness was an infectious process.

However, there were 16 instances in which the major illness was [illegible]

accurately because the symptoms were overshadowed by those of the major illness.

The Clinical Diagnosis.—The classical clinical features of acute glomerulonephritis are abnormal urine (albuminuria with casts, hematuria), oliguria, edema, hypertension and impaired renal function. There is no difficulty in the diagnosis when all of these signs are present, but in the absence of some of them there may be uncertainty. It is generally agreed that albuminuria must be present and that hypertension may be absent. It is also agreed that edema may be absent. An increased number of erythrocytes in the urine is demanded by the majority of clinicians, yet it seems unnecessary to insist upon this finding if all the other features are present.

Murphy and Rastetter make the diagnosis on the basis of albuminuria, hematuria and casts. There is little doubt that some mild cases of acute glomerulonephritis have only these findings [illegible]

nephritis indicates that the acute attack may be so mild that it escapes attention.

It is important to remember that hematuria in the absence of edema, hypertension and renal insufficiency, especially in a child, usually indicates benign hemorrhagic nephritis—a much milder disease than the proliferative form.

Pathological Anatomy.—There are 60 cases of uncomplicated acute proliferative glomerulonephritis and 34 cases in which the nephritis was a terminal complication of another disease. However, the two groups may be discussed together since the structural changes are identical.

The kidneys are usually enlarged, the combined weight in 79 [illegible]

and cloudy. On the basis of the macroscopic appearances alone

a diagnosis of acute nephritis cannot be made with certainty, since many kidneys with simple cloudy swelling show similar features

Microscopically under low magnification the glomeruli appear very cellular and few or no erythrocytes are to be seen (Fig 26).



Fig 26 —Acute proliferative glomerulonephritis. Note large cellular glomeruli and normal tubules Photomicrograph low magnification



[illegible] moderate [illegible] A few [illegible] Photo- [illegible] micrograph

There is obviously a great increase in the number of nuclei The diameter of the glomeruli is usually greatly increased but sometimes there is only a moderate increase in size

Under moderate magnification it is seen that the glomerular capillaries are filled with nucleated cells (Fig 27) The process is diffuse and in severe cases practically all the capillaries in all the glomeruli are occluded However in less advanced cases in which death was not due to uremia the obstruction is less uniform and a

these cells is indicated by their attachment to the inner surface of the basement membrane I have been unable to find mitoses in them but Hartz and associates have published good illustrations of mitotic figures and it therefore seems established that the process is a proliferative inflammation involving the glomerular capillary endothelium A varying proportion of polymorphonuclear leukocytes is found in over two thirds of the cases The polymorphonuclears are sometimes quite prominent but the obstruction is due largely to the mononuclear cells

Special Histological Features —In addition to endothelial proliferation which is invariably present there may be other changes (*a*) Epithelial crescents A few epithelial crescents may be found in a majority of the cases but occasionally they are so numerous that they overshadow the endothelial proliferation (Nos 2 3 24 26 60 Table 16) and this type may appropriately be called extra capillary glomerulonephritis When the glomerulus is compressed by a crescent there is much less endothelial proliferation but the capillaries are obstructed by external pressure (*b*) Thromboses Thromboses of afferent arterioles or of glomerular capillaries were found in a few cases (Nos 24 25 49 and 53 Table 16 Nos 12 22 and 2 Table 17) (*c*) The wire loop lesions said to be characteristic of acute lupus erythematosus were found in 2 cases (No 25 Table 16 and No 25 Table 17) (*d*) Casts Sometimes casts play an important contributory role in the production of renal insufficiency but they are seldom of major importance

An unusual anatomical picture was found in a recent case not listed in the tables A man fifty years of age died of uremia after an illness of three weeks which was typical of acute glomerulonephritis

urea nitrog

575 gm

glomerular

obstructed

glomerulonephritis

Pathogenesis —In various infectious processes notably bacterial endocarditis and puerperal endometritis there is often a rather

marked endothelial proliferation which differs from clinical acute glomerulonephritis chiefly *in the degree of capillary obstruction* (Figs 28 and 29) I have called this stage subclinical glomerulonephritis (Bell 1936) Apparently glomerulitis of this degree is fairly common in certain infections and it is only when the capillary obstruction attains a fairly severe degree that the clinical signs of nephritis appear It will be noted in Figures 28 and 29 that the capillary *basement membranes are distinct and in this respect the* subclinical differs from the clinical stage



FIG 28 Subclinical acute glomerulonephritis from a case of bacterial endocarditis *The endothelial cells are greatly increased in size and number but they do not obstruct* the capillaries completely The basement membranes are unaffected *Photomicrograph*

An early stage of clinical glomerulonephritis is shown in *Plate I Upper* Since this patient died from edema of the lungs before the onset of uremia the capillary obstruction is not much more pronounced than in the subclinical stage The capillaries are partially filled with endothelial cells and it is to be noted that the cells lie on the inner surface of the basement membrane It is highly

PLATE I





UPPER.—Early stage of acute glomerulonephritis. Death from edema of the lungs before the onset of uremia. The endothelial cells have caused only partial capillary obstruction. Mallory-Heidenhain stain. Photomicrograph.

LOWER.—Acute glomerulonephritis with uremia. The capillary circulation is almost completely blocked. Note the beginning fragmentation of the capillary basement membranes in the centers of the lobules. Mallory-Heidenhain stain. Photomicrograph.

probable that this stage is reversible, and we may believe that clinical cases which terminate in complete recovery have a similar glomerular lesion

A later stage is shown in Plate I *Lower* In this instance death was due to uremia and the capillaries are completely filled with endothelial cells When this degree of obstruction has developed it is probable that the glomerulus cannot open up again and that it will subsequently become hyaline if the patient survives



Fig 29 The same as Figure 28 under higher magnification Photomicrograph

Along with the endothelial proliferation there is an injury to the deep surface of the capillary wall The basement membrane of the outer surface of the capillaries is intact but the inner layers are split into numerous pieces which appear as hyaline fibers (Plate I *Lower*) As the lesion progresses these hyaline fibers increase in number and become fused to form a solid mass in the center of the lobule (Plate II *Upper*) Unless the splitting of the inner basement membranes is followed from its earliest stages it may appear that the hyaline masses develop between the capillaries but when successive stages of the process are studied it is readily seen that the central hyaline mass is formed from fusion splitting and swelling of the capillary walls where they are in contact This is the manner in which so-called intercapillary lesions develop

probable that this stage is reversible, and we may believe that clinical cases which terminate in complete recovery have a similar glomerular lesion

A later stage is shown in Plate I *Lower* In this case death was due to uremia and the capillaries are completely filled with endothelial cells *When this degree of obstruction has developed* it is probable that the glomerulus cannot open up again and that it will subsequently become hyaline if the patient survives



FIG 29 — The same as Figure 28 under higher magnification Photomicrograph

Along with the endothelial proliferation there is an injury to the [illegible] basement membrane of the [illegible] but the inner layers are [illegible] as hyaline fibers (Plate [illegible]

the hyaline masses develop between the capillaries but when successive stages of the process are studied it is readily seen that *the central hyaline mass is formed from fusion splitting and swelling* of the capillary walls where they are in contact This is the manner in which so-called intercapillary lesions develop

type recover completely it is obvious that it must be separated from the proliferative type. The more favorable outcome of nephritis in children than in adults reported by nearly all observers is presumably due in part to the prevalence of the benign hemorrhagic form in the young. The available data (Table 18) indicate that from 5 to 10 per cent of the patients die during the acute stage. The percentage of those surviving the acute stage who ultimately recover completely varies greatly in different reports. It appears probable that complete recovery occurs in about 50 per cent of cases of typical acute proliferative glomerulonephritis. The first reports on war nephritis a few years after the close of the first World War indicated a high percentage of recoveries, apparently because the latent chronic form was not recognized, but later reports were much less favorable because many of the latent cases had passed into the active chronic stage.

The frequency of the latent or quiescent chronic form has not been noted carefully by many observers, but Longcope's accurate records show that about one-third of the patients develop this form of the disease.

TABLE 18. OUTCOME OF ACUTE GLOMERULONEPHRITIS

Author	Total number	Died in acute stage, per cent	Number followed	Latent chronic, per cent	Active chronic, per cent	Died in chronic stage, per cent	Recovered, per cent	Comment
Van Slyke et al 1930	3	0	23	47.8	8.7	1.7	21.7	
Rosemoller 1928	26	4	5	5	1	4	56	
Lytle and Rosenberg 1929	51	11.8	45	0	15.[illegible]	0	84.5	
Blackfan 1926	24	12.5	21	0	0	0	100	
Clausen 1925	10	19.6	82	0	10.9	0	89	
Guild 1931	180	15.5	34	0	26.5	0	73.5	
Ernberg 1911	40	0	40	0	0	0	100	Under 15 years old
Ernberg 1911	1[illegible]	0	16	25	0	0		15 to 30 years old
Hill 1919	49	4.1	47	12	0	0	8[illegible].3	
Longcope 1938	11[illegible]	6	118	3[illegible]	6.9	6	50	
James 1931	67	0	67	13.4	[illegible]	0	87.6	
Osman	50	0	5[illegible]	35.7	0	0	64.3	
Hume 1938	281*	not reported	91	44.7	7.1	2.5	45.5	War nephritis
Talerman 193[illegible]	27	7.4	5	48	0	[illegible]	59	
Gross 1929	211*	not reported	11	1.8	8.4	5	44.5	War nephritis
Murphy and Rastetter 1938	150	6	1[illegible]	0	41.7	0	58.3	
McPhee 1932	90	5.5	49	0	14.6	0	85.4	
Richter 1936	100	5	41	0	15.5	4	80.5	
Folkers 193[illegible]	68	8.8		0	19.6	24.4	56	
Hayman and Martin 1940		9.1	5[illegible]	1.3	9.6	5.8	67.3	
Murphy and Rastetter 1938	15	15.1	130	0	35.1	0	49.[illegible]	

* Deaths during the acute stage not included

Other Forms of Acute Glomerulonephritis.—B *Exudative Type* (Fig 30).—This form of nephritis is associated with a severe staphylococcic infection which usually overshadows the renal symptoms There are 3 cases of this type in our collection In 1 case renal insufficiency was demonstrated and in another there was severe oliguria The glomerular capillaries as well as many of the tubules were filled with polymorphonuclear leukocytes There are transitions between this lesion on the one hand with renal abscesses and on the other with the proliferative lesion In two of our proliferative



Fig 30.—Acute exudative glomerulonephritis The glomerular capillaries are filled with polymorphonuclear leukocytes Photomicrograph

cases (Nos 51 and 58 Table 10) polymorphonuclear leukocytes were more prominent than endothelial cells Presumably a chronic nephritis does not develop from the exudative lesion

C *Hemorrhagic Type*.—This form of nephritis is characterized clinically by a marked hematuria We may distinguish a benign form and a severe form (1) Benign hemorrhagic nephritis was first described by Baehr The patient usually a child sometimes a young adult develops hematuria shortly after a sore throat or other respiratory infection There are no symptoms of nephritis

severe hemorrhagic type the clinical picture is bacteriemia with severe hematuria and uremia There are 11 examples of this form in our records In 6 of 7 cases in which blood urea nitrogen was



Fig 31 —Severe acute hemorrhagic glomerulonephritis from a case of bacteriemia The capsular spaces and tubules are filled with erythrocytes Photomicrograph

but there is no capillary obstruction The tubules are injured but their cells are not necrotic There is extensive filling of the tubules with erythrocytes and this obstructive lesion is probably the main cause of the renal insufficiency

D *Focal (Thrombotic) Glomerulonephritis* —Since Lohlein s publications in 1906 and 1910 it has been known that focal glomerular lesions may be found in association with bacterial endocarditis In his first paper Lohlein interpreted the lesions as capillary thromboses but in his second publication he explained them as small infarcts *resulting from the lodgment of minute infected emboli detached* from the valves of the heart Both Baehr and Fahr agreed with the latter interpretation

Baehr has made important contributions to this subject in a series of papers published from 1912 to 1923 He believes that only subacute streptococcus endocarditis is associated with embolic

lesions In 75 *cases of rheumatic endocarditis* Baehr and Sacks found no embolic lesions but they mentioned 2 cases with thromboses of capillary loops

Miller and Branch described typical embolic lesions in a case of endocarditis of fifty days duration caused by a hemophilic bacillus resembling H Influenzae In our experience embolic lesions are usually caused by Streptococcus viridans but may also be produced by Streptococcus hemolyticus



Fig 39 —Fresh hyaline embolic lesion The outlines of the thrombosed capillaries are easily visible and some of their basement membranes may be identified The thrombotic material stains red with azocarmine Photomicrograph

Embolic lesions may also occur in the absence of endocarditis (Baehr 2 cases Fahr, 1 case) In our autopsies there are 3 cases with numerous large lesions of embolic type in the absence of endocarditis In these individuals the clinical course was that of sub-acute glomerulonephritis

Hyaline thrombi in the glomerular capillaries are frequently seen when there is no endocarditis *In one instance of tuberculous* peritonitis in a male sixty-one years of age a large majority of the glomerular capillaries were occluded by hyaline thrombi and a

similar lesion was found in a child, five weeks of age, dead of congenital syphilis These hyaline thrombi correspond in structure with the fresh so-called embolic lesions found with endocarditis There is no associated necrosis of the capillary walls but many of [illegible]

occasionally a number of thrombosed glomerular capillaries

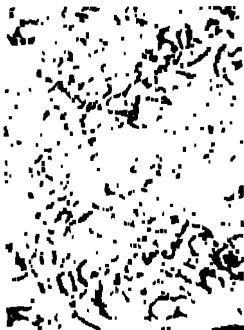


Fig 33 Hyaline embolic lesion that has undergone necrosis and is disintegrating The capillary walls are no longer visible Mallory Heidenhain stain Photomicrograph

In a previous publication (Bell 1932) the incidence of so-called embolic glomerular lesions in the various forms of endocarditis was reported as follows rheumatic, 2 9, acute primary bacterial (less than six weeks duration), 7 1 subacute bacterial 52 8 and secondary acute bacterial, 5 8 per cent All hyaline capillary thrombi were considered fresh embolic lesions The rheumatic lesions were all capillary thrombi without necrosis of the capillary wall

Two distinct types of lesions are found in association with bacterial endocarditis, the fresh hyaline and the fibrous With the

azocarmine stain the former are colored bright red, the latter a deep blue

1 The fresh hyaline lesions In its simplest form this lesion is a hyaline intracapillary thrombus A homogeneous mass is found which distends a long segment of the capillary but does not cause necrosis of its walls In larger lesions, however, there is necrosis of the capillary walls but one may often trace the outlines of the thrombosed capillaries (Fig 32) In old lesions all capillary outlines may be lost The lesion is usually restricted to one glomerular lobule, but not infrequently there are multiple capillary thrombi



Fig 34 —Fibrous embolic lesion The fibrous area stains blue with azocarmine Photomicrograph

and rarely the entire glomerulus is thrombosed The typical large lesions are clearly of the same nature as the small intracapillary thrombi

A study of the pathogenesis indicates that the process is capillary thrombosis and not embolism *The glomerular lobules are not infarcted in the sense that the blood is cut off from distal areas by occlusion of a proximal branch It is doubtful whether infarction* of a glomerulus can be produced in any way other than by occlusion of its afferent arteriole The lesions are presumably produced by the lodgment of minute infected emboli or *small clusters of bacteria* in the capillaries Toxic substances formed by the bacteria then cause thrombosis and necrosis The *focal character of the lesion*

indicates that the bacteria themselves lodge in the capillaries and in rare instances bacteria may be found In the case of embolic lesions without endocarditis one may believe that bacteria taken up by polymorphonuclear leukocytes destroy the leukocyte and then produce a local lesion

The fresh hyaline lesions become necrotic, disintegrate and disappear (Fig 33) They do not become converted into the fibrous lesions

2 The fibrous lesions are less frequent than the fresh hyaline and require a somewhat longer time to develop since they are seldom seen in acute endocarditis The lesions vary from small fibrotic areas to diffuse fibrosis of the entire glomerulus (Fig 34) Their fibrous structure is best shown by the azocarmine stain The fibers are derived from proliferation of capillary basement mem branes there is no organization of a preexistent lesion The fibrous lesions are not related to the fresh hyaline lesions but are comparable to some of the glomerular lesions of subacute glomerulonephritis

When a patient with bacterial endocarditis develops uremia it is usually due to diffuse glomerulonephritis but we have several cases dead of uremia in which the lesions were largely of the embolic pattern

In kidneys with extensive embolic lesions there are usually numer ous epithelial crescents usually fresh but sometimes old (fibrous)

streptococci In cases of staphylococcic endocarditis one finds *chiefly small glomerular abscesses and only an occasional fresh*

may occur in bacteriemias without endocarditis The bacteria most frequently produce capillary thrombosis (the fresh hyaline lesion) but focal fibrous lesions may develop (the fibrous embolic lesion) The embolic lesions are rarely extensive enough to produce renal insufficiency

2 **Subacute Glomerulonephritis** (Table 19) —This group blends on the one side with the acute and on the other with the chronic form and its limitations are arbitrary Clinically cases that begin acutely and terminate in uremia from three to twelve months after onset are usually called subacute Pathologically the kidneys are not contracted they may be of normal size but are usually enlarged Microscopically there is in most instances a severe involvement of all the glomeruli with a well marked diffuse tubular atrophy (Fig 35)

Example of subacute glomerulonephritis (Case 8 Table 19) —Clinical history

ber 16 1c

attacks o

the year



Fig 35 Subacute glomerulonephritis Nearly all the glomerular capillaries are completely closed and there is severe diffuse tubular atrophy Photomicrograph

It will be noted in Table 19 that there is no special age distribution There was nearly always a fairly severe albuminuria and some degree of edema was present in all but 4 cases In cases with severe edema and low plasma proteins the distinction from lipoid nephrosis is difficult until the terminal rise of blood pressure or of blood urea occurs (Nos 1, 2, 3, 5 and 15) In Case 15 death was due

to edema of the lungs The plasma proteins were decreased moder-

venous pressure

Blood cholesterol was markedly elevated in 4 of the 6 cases in which it was determined High cholesterol appears to be related to low plasma proteins



Fig 36 —Subacute glomerulonephritis Extensive focal fibrous lesion resembling those of endocarditis Mallory Heidenhain stain Photomicrograph

The blood pressure was elevated in 22 of the 27 cases in which it was recorded and very high pressures are frequent Some of the low pressures may be due to terminal events

Often there is a severe oliguria in the terminal stages with a rapid rise of blood urea Uremia was the chief cause of death except in No 10 with an abscess of the lung and No 15 with severe pulmonary edema There is usually a fairly severe anemia Onset following an infection was noted in only 4 cases

In 18 of the 34 cases the combined weight of the kidneys was above 350 gm which is about the upper limit of normal, and in 7 cases the weight was 500 gm or above The external surfaces were smooth there was no pitting or contraction

The microscopic structure varies widely By definition there is a fairly uniform involvement of all the glomeruli with moderate diffuse tubular atrophy Usually there are no hyaline glomeruli, but

TABLE 19 —SUBACUTE GLOMERULONEPHRITIS U N BLOOD UREA NITROGEN MG PER CENT CR CREATININE P P PLASMA PROTEINS PSP 2 HR EXCRETION OF PHENOLSULPHONEPHTHALEIN

Serial No	Autopsy No	Age	Sex	Duration	Blood pressure	Albuminuria	Edema	Renal function	Weight of heart gm	Weight of kidneys gm	Passive congestion of liver	Hemoglobin gm or %	Epithelial crescents	Comment
1	41 108	22 mo	M	8 mo	124 64 140 86	4	2	U N 145 (6 da.)	60	110	0	35%	2	P P 3 16 gm Cholesterol 500 to 1300 mg
2	47-94	30 mo	M	5 mo	115 80 168 130	3	1	U N 14 (6 wks.) U N 175	91	R80 L240	0	9 gm	0	Wilms tumor of left kidney cholest 628 mg P P 3 5 gm casts 4
3	46 1657	3	M	5 mo.	112/70	3	3	U N 66 PSP 11	—	180	1	4 gm	0	Cholest 451 mg P.P 4 gm
4	40-413		M	2 mo.	140 100	2	3 0	U N 49 U N 1 3	170	440	0	74%	4	Periarteritis nodosa cholest 219 mg P P 5 5 gm.
5	47 1715	7	M	10 mo	116 90 17 140	3	4	U N 32 U N 113	210	2 5	0	—	0	Cholest 960 mg P P 4 1 gm Casts 4 Severe ascites
6	25-798	8	F	2 mo			2		149	224	0	—	4	
7	39-2470	15	M	2 mo	144 110	1	1	U N 60	3 5	600	1			
8	3 193	16	M	3 mo	19 112	4	3	U N 7	360	710	0	58	2	Casts 4 P P 4.2 gm
9	30-156	16	M	7 mo	18 114	4	3	U N 116 PSP 0	3 8	285	0	45	1	Retinitis hyal glom Arteriolar thromb
10	40-825	16	F	7 mo	90/70	4	0	U N 39	240	440	0	44 %	0	Onset with peritonsillar abscess Abscess of lung. P.P 6 4 gm
11	31 1508	17	F	6 mo	200 112		3	U N 56	390	2 5	2	—	1	Retinal detachment
12	18-118	21	M	7 mo	14 80	1	2	U N 14 6 mo)	375	4 5	1—	—	3	
13	18 237	22	F	4 mo	220 120	3	3	U N 33 12 da	300	260	2	—	3	
14	48-504	22	M	1 mo	100/70 9 da	2	1	U N 280	300	375	0	5 8 gm.	4	Hematuria, Anuria
15	46 2140	23	F	5 mo	142 90 190 110		4	U N 26	4 5	425	0	6 gm	0	Death from edema of the lungs
16	22-363	3	M	3 mo +	—	2	1	U N 153	330	4 5	1	50	4	
17	41 2535	23	M	4 mo	140 80	4	1—	U N 1 5	350	470	0	24	4	Casts 4
18	13-8	26	F	3 mo		2	1		Norm.	Norm.	0	—	4	Severe hematuria
19	44 1685	28	F	3 mo	112 78		0	U N 57	315	4 8	0	12 gm	4	Severe otitis media embolic lesions P P 6.5 gm. Cholest 158 mg
20	3 1434	32	M	2 mo	155 95	3	3	PSP 4	540	535	0	23%	3	
21	12 131	33	M	3 mo		2	1		460	415	2	—	1	
22	16-138	30	M	5 mo		3	3	U N 104 PSP 0	3 5	250	0	35	2	
23	25-945	41	M	2 mo	248 102	2	2	U N 80 7 wks		335	0	—	2	Embolic lesions. No endocarditis
24	25-8 8	44	M	10 mo	180 120	4	3	U N 5	315	315	—	90%	0	Onset with head cold
25	39-767	48	M	2 mo +	19 90	3	0		450	3 5	0	65	0	Embolic lesions. No endocarditis
26	34 584	50	M	5 wks		4	1	U N 16	270	370	0	80%	2	
27	15-253	51	M	4 mo	1 2 100	2	3		3 5	300	—	—	1	Many hyal glomeruli
28	47 1516	52	F	1 yr	18 90 180 100	3	0	U N 90 Cr 11	4 0	330	0	8 gm.	2	Onset with otitis media
29	19-5	53	M	1 yr	20 120	2	2	PSP 0	470	590	0	—	1	Retinitis hyal. glomeruli
30	30-415	5	M	3 mo	150 95 18 130	4	2	U N 140	430	300	1	30%	1	Retinitis hyal glomeruli
31	45-1634	61	M	3 wks	170 90	3	1	U N 1 1	4 5	365	0	90%	4	Oliguria. Anuria
32	35 259	6	F	1 mo. +	200	2	2	U N 6	350	250	2	—	4	
33	11	70	M	—	—	2	3		4 5	335	0	—	2	Hyal. glomeruli
34	45 23 8	73	F	7 wks	1 4 95	3	1—	U N 120	460	3 3	0	8 gm.	0	

in cases of long duration some glomeruli have reached the hyaline stage The distinction from chronic nephritis cannot be made microscopically when many hyaline glomeruli are present but the clinical history may establish the duration of the disease Epithelial crescents are usually conspicuous and in 9 cases they were almost entirely responsible for the glomerular obstruction In two cases (Nos 2 and 8) uremia was due chiefly to the presence of enormous numbers of casts

Local fibrous lesions were found in 8 cases and in 2 instances

membranes

In Nos 23 and 25 there were numerous hyaline capillary thrombi identical with fresh embolic lesions of bacterial endocarditis In fact No 23 shows all the typical features of embolic glomerulo-

branes resemble those found in lupus erythematosus

Proliferation of the intracapillary endothelium was always present to some extent but often it was subordinate in importance to the epithelial crescents In Nos 27 29 30 and 33 there were many hyaline glomeruli and the appearances were not different from those of chronic glomerulonephritis In fact these cases are put in the subacute group largely on the basis of the clinical history

The tubules show atrophic changes which vary directly with the degree of obstruction of the associated glomeruli When the glomerulus is completely obstructed its associated tubule is markedly atrophic (Fig 35) with only moderate obstruction of the glomerular

sidered for a time because of the massive edema the low plasma proteins and the high blood cholesterol but later the rise of the blood urea and the increase of blood pressure suggested glomerulonephritis Retinitis is usually observed in those with very high blood pressure

3 **Latent Chronic Glomerulonephritis** (Table 20) —The 6 cases listed in Table 20 are examples of chronic glomerulonephritis in which death was caused by another disease before marked renal insufficiency had developed These cases are of particular interest

of the kidneys in the pre-uremic stage of chronic glomerulonephritis

TABLE 20.—CHRONIC GLOMERULONEPHRITIS IN WHICH DEATH WAS DUE TO AN INTERCURRENT DISEASE (LATENT CHRONIC TYPE)

Serial no	Autopsy no	Age	Sex	Duration of symptoms	Blood pressure	Albuminuria	Edema	Urea nitrogen mg per cent	Phenolsulphonephthalein	Weight of heart gm	Weight of kidneys gm	Hemoglobin per cent	Hyaline glomeruli per cent	Cause of death
35	31 704	23	F	3 yr	140/90 (3 yr) 150/90 (5 da)	4	0	—	61 (3 yr)	—	Large	—	10	Tetanus following induced abortion
36	33 293	34	F	?	170/90	4	1	28 (2 da)	—	420	462	70	10	Ulcerative colitis
37	37 670	41	M	6 wk	140/90	3	0	38 (18 da)	—	375	325	—	0	Subdural hematoma
38	27 511	43	F	?	110/70	1−	1	—	—	538	304 (one)	—	0	Cardiac failure
39	28 1110	58	F	?	—	1−	0 2	—	—	215	195	40	0	Ischiorectal abscess
40	34 1408	80	F	?	138/90	1	1	15 6 (1 da)	—	450	250	58	5	Purulent bronchitis

is one by Dorothy Russell in 1934 She described a kidney removed under an erroneous diagnosis sixteen years before death The remaining kidney at autopsy showed a typical advanced chronic glomerulonephritis The illustration of the kidney removed sixteen years before death is shown only under low magnification but resembles those which I am reporting

A clinical diagnosis of chronic glomerulonephritis was made definitely in Case 35 and the disease was suspected in Nos 36 and 37 in the others it was made from a histological study of the kidneys since the renal symptoms were overshadowed by those of the major disease In Case 36 the clinical picture was that of ulcerative colitis but there was a severe albuminuria The mild edema may have been due to emaciation Case 38 was regarded clinically as cardiac hypertrophy and heart failure resulting from primary hypertension In Case 39 there was an ischiorectal abscess of four years duration as well as severe emaciation There was only a trace of albumin in the urine and the edema developed terminally

There was some evidence of renal injury in all of the patients but there was no serious impairment of renal function

The clinical history in Case 35 will be given in detail since this case is a good illustration of the group under discussion I am indebted to Dr George Fahr for the excellent clinical record which follows

Th

no edema The diagnosis was acute glomerulonephritis The patient

this time

At postmortem the kidneys were found to be enlarged with smooth external

but the capillaries are not markedly constricted The peripheral capillary basement membranes are *not thickened* Glomerular filtration is evidently fairly good since there is no atrophy of the tubules associated with these glomeruli

The structural changes in the kidneys of the other 5 cases correspond to the above description with minor variations The kidneys are not contracted but are usually somewhat enlarged In Case 36 there were some old epithelial crescents, the capillary obstruction was more pronounced than is shown in Plate II, *Lower*, and Figure 37, and had resulted in slight tubular atrophy.



micrograph

The glomeruli of the pre-uremic stage are *similar in structure to* the functioning glomeruli of the active chronic stage.

4 **Chronic Azotemic Glomerulonephritis.**—For purposes of study the chronic cases have been subdivided into groups in accordance with certain clinical and pathological features There are 51 cases with a definite history of an acute attack. In 27 of these (Table 21)

TABLE 21*—SUBGROUP 1 CHRONIC AZOTEMIC GLOMERULONEPHRITIS IN WHICH THE ACUTE STAGE PASSED DIRECTLY INTO THE ACTIVE CHRONIC FORM

Serial No	Autopsy No	Age	Sex	Duration	Initial infection	Blood pressure	Edema	Renal function	Weight of heart gm	Weight of kidneys gm	[illegible]	Hemoglobin % or gm.	Retinitis	Comment
41	42 1223	10	M	1 yr	Sore throat	110/78 (1 yr) 140/110	3	U N 50 154	155	21(R) 12? L)	1	96% (1 yr)	0	3 attacks of peritonitis Cholesterol 497 mg P P 4 3 gm
4?	47 1038	10	M	18 mo	A cold otitis media	138 100 18? 122	4	U N 105	2?0	240	0	8 gm	—	Cholesterol 2?8 mg P P 4 9 gm Ca 4 mg
43	41 1061	13	M	4 yrs	Mastoiditis	137/96	2 0	U N 42 170	170	309	0	46%	—	P P 6 7 gm
44	39-636	13	M	1 yr	Pneumonia	164 ?	1	U N 216	3?0	Small	0	23%		Single kidney also pyelonephritis P P 6 1 gm Cholesterol 2?9 mg
4?	3? 2064	15	M	4 yrs	—	220/110	2	NPN 28?	390	460	0	59%	—	
46	36 2143	15	F	1 5 yrs	Tonsillitis	145 100 170 130	4	U N 34 (18 mo) U N 119 PSP 0	4?0	160	2	54%	—	P P 5.5 gm
47	39-177	16	M	14 mo	Upper respiratory	114/80 20? /130	2 0	U N 42 98	471	340	0	40%	—	P P 4 8 gm
48	43 2142	16	F	15½ yrs	—	170/14? 226 150	0	U N 36 64	450	140	1	—	—	Acute attack at age of 4 months P P 7 4 gm
49	47 2?98	18	M	9 yrs	Measles	140/80 (2 yrs) 1?? 120	0	U N 17	400	160	0	7 8 gm	—	
50	31 1974	19	M	9 yrs	Scarlet fever	190 110	1 0	U N 110 ?38	550	?00	0	28%	—	
51	34 763	19	F	4 yrs	A cold	190/118	2 0	NPN 218	3?0	1?0	2	40%	+	Exacerbations P P 5 4 gm
52	33-1150	21	F	14 yrs	Scarlet fever	160/100 230 100	2 0	NPN 3?7	325	100	1	3? %	0	Cholesterol 158 mg
53	28 1?0	21	M	3 yrs.	—	2? /160	2 0	U N 28 U N 119	420	174	1	60%	—	
54	41-936	2?	F	5 yrs	Upper respiratory	165 100 (3 yrs) ?10/14?	1 4	U N 77 (3 yrs) U N 154	400	1?0	3	3?%	+	Severe exacerbation during pregnancy Therapeutic abortion
55	48 519	23	M	3 yrs		160/12?	4	—	4?0	310	0	—	—	Albuminuria 4 Hydrothorax 3500 cc Transition to lipoid nephrosis
56	27 45?	24	M	18 yrs	—	158 80	1—	U N 97 PSP 0	320	135	—	16%	+	
57	23-48	25	M	9 yrs	Measles	210 140	0	U N 165	—	163	—	3?%	+	
58	17 6?	27	F	8 yrs	—	160/? (8 yrs) 185 1?0	1 2	U N 101 PSP 0	455	150	0	40%	+	
59	30 1019	29	M	3 5 yrs	—	245 140	1	U N 102 PSP 0	590	300	—	52%		P P 5 4 gm cerebral hemorrhage
60	27 261	31	M	1 yrs	Sore throat	190 90	1 0	U N 260	420	175	1—	4? %	+	Oliguria
61	48 1?8	3?	M	2 yrs	—	162/112	0	U N 2?5	550	2?0	0	3 7 gm.	0	Ca 7 5 mg P 19 5 mg
6?	30 958	33	M	1? yrs	Sore throat	270 ?	4	cr 15	625	1?5	—	50%		
63	41 1 58	41	M	30 yrs.	Scarlet fever	13? 80 155 95	3	U N 57	3??	4?0	3	34 %		Death from aortic stenosis exacerbations P P 6 1 gm. Cholesterol 215 mg.
64	31 1146	44	F	4 yrs.	—	—	0	PSP 0	3?0	200	0			Casts 4
65	46-453	4?	M	31 yrs	Influenza	140/? 190/110	1	U N 30 1?2	800	220	0		—	Recurrent acute (5 yrs) P P 6 gm Ca 7 5 mg P 10 mg
66	33-867	53	F	5 yrs.	A cold	18? 106	2 0	NPN 163	450	140	0	34%	0	
6?	34 10?4	6?	M	34 yrs		13? 98 (6 yrs) 160/120	1—	NPN 112	6?5	120	0	—		

* Abbreviations P P total plasma proteins, gm per cent U N blood urea nitrogen NPN non-protein nitrogen cr creatinine P phosphorus Ca calcium, mg per cent PSP phenolsulphonephthalein (2 hour excretion

TABLE 22.—SUBGROUP 2 CHRONIC AZOTEMIC GLOMERULONEPHRITIS WITH A LATENT PERIOD BETWEEN THE ACUTE AND THE ACTIVE CHRONIC STAGES

Serial no.	Autopsy no.	Age	Sex	Duration: Total	Duration: Acute chronic	Initial infection	Blood pressure	Edema	Urea nitrogen, mg. per cent	Non-protein nitrogen, mg. per cent	Phenolsulphonphthalein, %	Weight of heart gm	Weight of kidneys gm	Passive congestion liver	Hemoglobin, %	Retinitis	Comment
68	25-246	16	F	4 yr	16 mo	Sore throat	180/130	2	70 (1 mo)	—	0 (1 mo)	400	163	1−	38	+	
69	23 846	18	M	2 yr	1 mo	—	200/134	1	181 (2 hs)	—	—	475	245	1−	50	+	
70	40 718	18	M	3 yr	5 wk	A cold	202/140	0	124	—	0	480	275	0	30	+	Congenital hydronephrosis; acute stage lasted 8 months; total protein 8 8 gm
71	40 1476	18	F	9 yr	6 yr	Mastoiditis	135/75 (6 yrs) 232/120	0	52 (3 mo) 140	—	—	340	88	0	60 (3 mo) 20	+	
72	36 1587	20	M	10 yr	2 yr	Common cold	130/125 (1 mo)	1	—	171 (1 mo)	—	585	180	0	35	+	1 exacerbation
73	24 323	23	M	6 yr	6 wk	—	180/124	3 1	109	—	0	425	125	0	49	—	Single kidney
74	32 2026	26	F	8 yr	5 yr	—	195/140	2 0	200 (2 hs)	—	0 (6 wk)	475	210	1−	40	+	Exacerbations; toxemia of pregnancy
75	41 15	25	M	20 yr	6 mo	Scarlet fever	140/90	1	87	—	—	—	85	—	47	—	
76	38 875	26	M	16 yr	11 yr	Mumps	172/90 (11 yr) 240/160 (6 mo)	1 2	63 (6 mo) 89 (1 wk)	—	29 (6 mo) 0 (6 wk)	550	265	0	45	+	Repeated exacerbations; calcium 8 3 mg; phosphorus 8 6 mg
77	43 2029	27	M	21 yr	5 yr	—	192/120	3	140	—	—	[illegible]	240	0	[illegible]	+	
78	19 264	29	M	6 yr	2 mo	Common cold	170/80	1	87 (1 mo)	—	0 (1 mo)	435	340	1	25	+	

79	36 2304	29	M	14 yr	1 mo	Scarlet fever	170/110	1 0	27 (1 mo)	—	0 (1 mo)	540	180	0	74 (1 mo)	+	Single kidney
80	*30 1480*	*32*	*F*	*16 yr*	*11 yr*	—	142/92 (11 yr) 250/130	2	30 (1 wk)	—	60 (10 yr) 0 (1 wk)	350	100	0	75	+	Total protein 6.7 gm *cholesterol 218 mg*
81	18 117	32	M	10 yr	2 mo.	—	190/140	2 1	—	—	0 (2 wk)	630	405	2	—	—	
82	47 1523	32	M	25 yr	6 mo	—	176/90	1	130	—	—	450	130	2	45	—	Plasma proteins 6.8 gm.
83	33 2022	33	M	12 yr	3 mo	—	220/130	1 0	280 (3 da)	—	—	550	180	1	—	+	
84	41 2524	34	M	18 yr	1 yr	—	118/78 (7 yr) 170/120	0	147	—	—	480	150	0	36	+	Total protein 5.9 gm
85	34 267	35	M	16 yr	10 yr	Influenza	180/100	1	—	328 (3 wk)	—	575	190	0	36	+	Exacerbations
86	27 49	35	F	6 yr	5 yr	—	148/90 (3 da)	3	101 (1 da)	—	—	300	Small	0	30	0	Abortion (2 yrs)
87	31 241	35	F	23 yr	16 yr	Scarlet fever	225/135	1	80 (5 da)	—	4 (7 da.)	430	220	1	63 (7 da)	0	3 therapeutic abortions for toxemia
88	40-1644	35	F	33 yr	2 yr +	Scarlet fever	180/104	2	248 (1 mo) 60 (2 wk)	—	—	250	100	2	42	0	
89	35 562	40	M	9 yr	?	—	134/80 (3 da)	0	279 (1 da.)	—	—	546	177	0	36	0	
90	27-653	43	M	6 yr	5.5 yr	Sore throat	128/80 (6 yr) 200/120 (1 mo)	2	15 (6 yr) 150 (5 da)	—	—	700	195	1	—	Pr	
91	38 9	46	M	32 yr	1 mo	—	130/78 (1 da)	2	210	—	—	600	110	0	58	—	
92	30-1826	52	M	26 yr	1.5 yr	Tonsillitis	238/124	0 1	47.6 (6 mo) 74 (2 da)	—	25 (2 mo)	827	234	0	55	+	
93	30-1854	54	M	Many years	2 wk	—	170/100	0	140 (2 da)	—	—	524	187	0	40	0	Single kidney with double pelvis and ureter, many casts
94	37 1883	62	M	44 yr	18 yr	—	180/90 (18 yr) 220/110	0	—	—	—	525	105	0	—	—	

the acute stage passed directly into the active form and continued as such until death and in the 27 others (Table 22) the acute stage passed into a latent or quiescent period of variable duration which was then followed by the active chronic form

In 216 chronic cases no history of an acute attack could be obtained and this group has been subdivided in accordance with the size of the kidneys

GROUP A *Chronic Azotemic Glomerulonephritis With History of an Acute Attack* *Subgroup 1* *Chronic Azotemic Glomerulonephritis in Which the Acute Stage Passed Directly into the Active Chronic Form (Table 22)* —There are 27 cases in this group and it will be noted that the duration varied from one to thirty four years Fourteen patients lived less than five years and 11 lived over eight years The initial infections were similar to those found in glomerulonephritis which terminated in the acute stage (Table 16) Two thirds of the kidneys were contracted weighing less than 201 gm Since there were no other special clinical or pathological features the other data will be discussed with the group as a whole

Subgroup 2 *Chronic Azotemic Glomerulonephritis With a Latent Period Between the Acute and the Active Chronic Stages (Table 22)* — There are 27 cases in this group and the time between the acute attack and death varied from two to forty four years the average being fifteen years In 16 cases the duration was over ten years and in 8 cases over twenty years The duration of the latent period which may be obtained by subtracting the active chronic from the total duration varied from about two to over thirty years In several instances the active chronic stage lasted only a few weeks or a few months in others it is measured in years

The duration of the active chronic stage was necessarily based upon the statement of the patient with respect to the onset of his symptoms The patients were following their usual occupations and stated that they had been well up until the time indicated in the table In some instances this seems incredible and one must believe that the presence of the disease could have been readily established long before the time indicated by the patient In No 79 the patient dated the onset of his illness one month before death yet he had marked cardiac hypertrophy and severely contracted kidneys None of the patients was studied during the latent period so the status of renal function during this time is unknown It is highly probable therefore that the indicated latent period was not one of perfect health but merely a period without striking symptoms In Group B in which there is no history of an acute attack many patients likewise date the onset of the illness only a short time before death

In cases with an unusually long latent stage *e g* Nos 88 91 and 92 the question may arise as to whether the terminal chronic

Continued on page 189

TABLE 23*—SUBGROUP 3 CHRONIC AZOTEMIC GLOMERULONEPHRITIS WITHOUT HISTORY OF AN ACUTE ATTACK IN WHICH THE COMBINED WEIGHT OF THE KIDNEYS WAS 300 GM OR MORE

Series No	Autopsy No	Age	Sex	Duration of symptoms	Blood pressure mm Hg	Edema	Renal function	Weight of heart gm	Weight of kidneys gm	Thickening of [illegible]	Hemoglobin [illegible] gm	Retinitis	Comment
95	33 855	17	M	8 yrs.	9 8 130	0	U N 138	505	34		50°	+	Many casts Acute exacerbations
96	34 2199	18	F	4 yrs.	140 110	1	U N 39	2	300	0			
97	25–171	19	M	mo	128 60 (days)	0	—	3 ,	3 5				
98	48 9	19	M	5 m	14 9	0	U N 43 310	450	370		2 4 gm.		
99	22 118	20	F	3 yrs	19 154	0	U N 76 PSP 0	4 0	40	2	7	+	Exacerbations. Many crescents
10	36 2331	21	M	8 mo +	23 30	3 0		5 ,	325	1		+	
1 1	34 2102	22	F	5 mo +	—	1	PSP 20 (2 mo		300	0	59°	+	Cholesterol 210 mg No hyaline glomeruli
1 2	35 1131	24	F	1 yr	164 92	1 —	NPN 2	400	3 0	2	34°		
103	41 1 71	25	M	5 yrs +	13 80 5 yrs 2 4 13	1	U N 1 (4 yrs	42	315	)	38	+	P P 6 2 (5 yrs) Maximum concentration to 1013
104	48 2583	26	F	3 mo	19 110	4	U N 115 198	4	3 4	1	6 gm		Bacterial endocarditis Casts 4 Cholesterol 245 mg P P 5 9 gm
105	45 1319	28	M	3 yrs.	2 2 110 254 160	1		650	3 5	0	78	+	
106	45 2 3	29	M	5 yrs	18 110	1 0	U N 68	500	30	0	7 8 gm	+	P P 6 2 gm
1 7	33 5	3	M	10 yrs	115 70 (3 yrs 170 11)	)	NPN 176 PSP 0	53	40	0	60	+	
1 8	14 19	3	M		1	1		4 8	30				
1 ,	4 1517	31	M	9 yrs	164 11	1	U N 114	525	335	1	4		
110	4 23 8	31	M	6 yrs	13 9 1 yr) 19 120	1	U N 44 64 er 19	4 ,	41	1	9 4 gm.	+	
111	10–145	3	M			0		53	314	3	—		
11	15 67	35	F	3 rs +		1	—	40	Normal	0		+	
113	41 28 6	37	M	11 yrs	140 108 (1 yr 19 110	0	U N 4 5	53	5	0		+	
114	17 1 8	39	M	3 yrs	—	1		640	3 0	0		+	
115	41 15 1	41	M	Many yrs.	—	0	NPN 9	4 5	34	0	63°	+	Fresh crescents
116	10 2	43	M	1 yr	140 0	0	U N 1 5 PSP	Large	300	—	30	0	
117	4 1305	43	M	Several yrs.	156 109	2	U N 1 0	413	57	0	6		
118	34 1 4	45	M	1 yr +	160 110	0	U N 40 6 mo	610	31	1			
119	41 87	4	M	1 mo.	185 1 0	0	U N 1 2	5 ,	350	0	6	—	
12	32 454	50	M	6 yrs.	2 5/125	1	U N 82 PSP 5	60	455	2	4	+	
1 1	33 55	5	M	2 5 yrs	134 96 8 mo)	1	U N 60	519	452	0			Multiple myeloma Casts 3
1	15 394	54	M	2 mo	16 9	1 0		6 0	319	0			
1 3	35 9 6	54	F	1 mo	1 6 9 4 wks) 19 135	0	U N 75	45	3 0	0	—		
124	4 633	54	M	4 yrs +	235,110	0	U N 153	600	3 5	0	—		Fresh crescents 3 Anuria arteriolosclerosis
1 5	44 3 4	56	M	4 mo	18 106	2	U N 36	50	3 3	1	9 gm		Severe purpura for ? yrs Ascites. Hydrothorax
126	73 1 6	56	M	1 yrs.	154 110	1		500	4 5	1	—	0	
1	16 319	63	M			0		400	3	0			
1 8	41 27	64	M	2 yrs.	2 4 178	(	U N 46	5 5	45	0	—	+	
1 9	40 4	65	M	6 mo	14 8	1	U N 97 PSP 5	350	335	0	31	+	
13	48 2021	7	M	Indefinite		2	U N 39	4 0	400	0	gm.	—	Pulmonary tuberculosis
131	41 2355	4	M	8 mo.	130 7 15 82	0	U N 31 14	340	339		65%	—	

* Abbreviations as in Table 21

TABLE 24 — SUBGROUP 4 CHRONIC AZOTEMIC GLOMERULONEPHRITIS WITHOUT HISTORY OF AN ACUTE ATTACK IN WHICH THE COMBINED WEIGHT OF THE KIDNEYS WAS LESS THAN 300 GRAMS

Serial No	Autopsy No	Age	Sex	Duration of symptoms	Blood pressure mm Hg	Edema	Renal function	Weight of heart gm	Weight of kidneys gm	Passive congestion of liver	Hemoglobin % or gm	Retinitis	Comment
132	43 1216	7	M	Several yrs	148/104	2	U N 143	145	105	0	—	0	
133	40 1508	7	M	Indefinite	—	0	U N 60	95	41	0	—	—	Renal rickets Polyuria P P 8 7 gm
134	48 863	7	M	2 yrs	—	3	—	140	Small	0	10 gm	—	Severe edema with remissions Pneumonia
135	33 1854	8	F	1 yr	210/120	0	N P N 156	—	80	—	50%	—	
136	38 1730	8	M	6 yrs +	100/14 (6 yrs)	0	U N 149	200	30	0	68%	+	Bu gle kidney P P 7 6 gm
137	43 2231	13	M	5 yrs	225/165 140/80	1	PSP 0 U N 20 (5 yrs)	325	(R)80	0	—	—	Left kidney removed Cholesterol 195 mg P 13 mg
138	40 2363	13	F	2 yrs	150/120	2	U N 283 U N 135 cr 13	370	230	0	7 6 gm	—	Cholesterol 275 mg P P 4 6 gm
139	30 519	14	F	1 yr +	—	1 —	U N 176	170	185	0	43%	—	
140	41 231	14	F	1 yr +	145/90	0	U N 166	180	110	0	44%	—	
141	46 2707	16	M	9 mo	170/90	1	U N 111	303	(R)63	0	8 6 gm	—	Hydr thorax 1000 cc P P 7 7 gm Ca 7 5 mg, P 8 2 mg
142	32 540	17	F	2 mo	160/130	1	—	330	54	0	52%	+	Single kidney
143	43-1 [illegible]	17	F	5 mo	200/120	2	U N 176	413	250	1	7 4 gm	—	Upper respiratory infection (2 mo) P P 7 8 gm
144	43 1405	18	F	Many yrs	—	0	U N 179	—	90	—	45%	0	Ascites 2,000 cc Never menstruated P 9 5 mg Ca 5 mg
145	44 1279	18	F	Many yrs	140/90	1 0	U N 141	300	90	0	53%	—	
146	42 844	19	F	11 yrs +	165/120	1	U N 140	385	80	0	45%	+	P P 7 9 gm
147	43 2	19	F	1 yr	130/115	1	U N 195	325	150	—	—	—	Single kidney
148	46 1642	19	F	18 yrs	198/120	0	PSP 0	270	(R)60	0	39%	—	Severe left hydronephrosis Atresia of ureter
149	47 1541	19	M	2 yrs	130/105	1	U N 108	400	205	0	4 0 gm	—	Severe ascites P P 2 6 gm
150	32 1053	20	M	1 yr +	210/130	1	U N 111	380	77	0	45%	—	
151	42 928	21	M	4 mo	145/100	0	U N 182 300 PSP 0	310	73	0	42%	—	
152	38 2370	21	M	—	168/118	0	PSP 2	440	250	—	—	—	
153	41 2803	21	M	Many yrs	180/120	0	U N 244 cr 14	520	220	0	—	—	

154 155 156	45 2248 37 1 42 449	21 22 2	M M F	7 m 1 m +	180 1 4 168 144 1 1 82	))	L N 1 4 L N 11 L N 12 8	4 41 3 8	100 118 80	0 0 0	37%			O teom el t s for 9 m gle k dney h fro ef bros s I ss ble a u e attack at age of 8 y s
157	41 38	2	F		2 m 1									
158 1	15 773 41 174	3 23	M M	5	1 110 165 100	3 2	3 m L N 1 L N 77							
1 0	46 1033	3	M	3 n 4 y s +	71 140 18 115									
1 1	36 871	3	M	mo	13 96 19 130	1 0	2 m L N 1 4 L N 11	4 8	130	3				
162	41 1749	23	M		214 145	0	L N 89	5 7 38	small					
163	16 384	23	M	2 s +	134 120	0	L N 10	10		0	30%			
164 165	83 214 47 131	4 24 4	M M	2 m + 3 mo	1 0 1 8 1 8 13 170 8	0	L N 19 L N 161 L N 0 L N 17	440	1 80	1 0	11 gm 45%	+	0	I sed pels e k lne I P 6 6 gm I 11 mg Ca 8 mg
166	48 1680	25	M	1 mo	189 10	1	2 m L N 68	395		0				I I 5 8 gm
167 168	32 047 37 1 4 1	25 25	M M	16 5	18 110 H gb	1 0	L N 131 L N 0	415	9	0				L lateral f se l k l e
169 170	27 1987 19 2	25 21	M M	6 wks +	1 0 7 1 16 9 08	1 0	U N 200 U N 204 U N 31	4 0 4 0	87	0	0%			
171 172	40 1318 41 1832	21 25	M M	3 n o 0 n	70 1 8 210 118	1 2 0	U N 180 L N 29 L N 240 L N 1 0	380 380 4 0	13	1	90% 0 6 gm			
173	0 766	20	F	1 n o 1 d 6 le	220 1 0 19 1 0		L N 82 118 L N 72	325 500	14 1 2		6 gm 4% 36%			Asc ca 1 800 cc I I 6 0 gm I mg (a 7 5 n g bea let f e at age of 8 y s I I 8 7 gm (a 7 n g I 15 n g
174 175	73 431 41 1 13	26 6	F F	4 m	160 110 3 m 1 21 170	1 0	L N 0 L N 24 L N 211 L N 0	680 415	05 1 5	0	6 %	0 + +		I I 6 5 gm
176 177 178	4 473 24 1 1 22 47	26 27	F M	4 m 6 m +	H gb 134 9 5 m 1	0 0 2	3 m 2	380	00 18 21 1	0 2	7 % 4 %	+		
179 180 181 182	32 1 35 16 132 43 1 187 45 24 5	27 7 22 27	M M F F	2 ms 2 5 10 m 3 u 2 m + Ma m	21 1 14 11 1 18 24 18 1 8 1 4 114 145 1 0 110	0 1 1 1 1 2 1	L N 9 2 m L N 243 L N 0 L N 134 L N 0 L N 216 L N 80 L N 1 7	375 111 308 200 54 1 6 0 4 480 3 5	12 4 80 52 110 75 1 0 1 0 1 8	0 1 0 1 0 1	4 % 33% 36% 43% 3 6% 6% 6 3 gm	0 +		Seve e sca let f ver el ldl ood I al ert n I toxe n a kare bat ons I oxe n a of i reg a (a 7 4 n g I I mg 4 y s) Dus t H poil s e k l e s Abscess of eck

TABLE 24—SUBGROUP 4 CHRONIC AZOTEMIC GLOMERULONEPHRITIS WITHOUT HISTORY OF AN ACUTE ATTACK IN WHICH THE COMBINED WEIGHT OF THE KIDNEYS WAS LESS THAN 300 GRAMS (*Continued*)

Serial No.	Autopsy No.	Age	Sex	Duration of symptoms	Blood pressure mm Hg	Edema	Renal function	Weight of heart, gm	Weight of kidneys gm	Passive congestion of liver	Hemoglobin % or gm	Retinitis	Comment
183	45-214	28	M	Several yrs	170/90	0	U N 313 cr 30	500	145	0	5 5 gm	—	Severe tonsillitis at age of 6 yrs Blood sugar 187 mg
184	45-1836	28	M	2 yrs	160/125	4	U N 282	400	80	—	7 7 gm	—	Severe ascites and hydrothorax
185	36-12	28	M	7 yrs	154/100 (9 mo)	0	U N 140 PSP 0	350	71	0	45%	—	
186	34 1467	28	F	6 yrs	185/80	1	—	325	80	1—	—	+	3 normal pregnancies
187	31 1135	28	M	11 yrs	218/140	0	U N 337 (6 wks)	475	145	0	0%	+	
188	44 301	28	M	10 mo	—	1 0	cr 15	710	240	0	34%	+	Sore throat (10 mo)
189	3?-1812	28	M	15 mo	215/148	1	U N 34 104 PSP 0	43	170	1	37%	+	
190	43 1131	29	F	9 yrs +	134/68 (9 yrs)	1	U N 70	500	75	—	40%	—	
191	28 1146	29	F	2 yrs	270/170 114/94 (2 yrs)	1—	PSP 0 U N 124	430	80	—	60%	—	1 normal pregnancy 1 abortion
192	37 2199	29	F	10 yrs	194/1 4 17 102 (2 yrs)	1	U N 80 203	425	113	—	36%	+	1 toxemia of pregnancy
193	22 574	29	M	10 mo	240 110 180 125	1 0	U N 142	370	230	0	56%	—	
194	37 304	29	F	8 mo	275 170	0	U N 339	340	175	0	54%	+	Thick basement membranes
195	48-1634	29	M	7 yrs	236/132	0	U N 270 PSP 0	480	200	0	7 gm	+	1 1 5 6 gm Oliguria
196	15 363	30	M	3 yrs	—	0	PSP 0	575	155	—	—	—	
197	31 1 47	31	F	5 yrs +	190/110	1	—	275	95	0	—	—	2 toxemic pregnancies
198	34 346	31	F	4 yrs +	170 90	0	N P N 267	570	280	1	64%	+	3 normal pregnancies
199	32 2099	32	F	—	130 60 (3 da)	1—	N P N 234	—	0	—	—	—	
200	19 160	32	M	—	170 80 (3 da)	0	—	350	140	0	—	—	
201	38 1044	32	F	20 yrs	205 110	3	U N 149	350	100	0	54%	—	3 abortions, 1 toxemia of pregnancy
202	28 1119	33	F	6 yrs	210 ?	0	U N 60 (2 wks)	340	120	0	4 %	—	
203	44 446	33	F	10 yrs	—	0	—	350	50	0	—	—	Severe otitis media intermittently

204	22 1 8	33	F	9 rs	154 92	1	U N 29 (2 wks)	3 0	230	0	0%		4 children during last 9 yrs
205	12 40	33	M	1 mo +	200 +	1 –		73	250	0		—	
206	9 2005	34	M	3 rs +	18 170	1	U N 184	3 0	95	0		+	
207	38 204	34	M	3 mo	230 170	1		42	59	1 –	—	+	
208	13 194	34	F	10 mo		0			Small				
209	41 181	34	F	4 rs	154 90	1	U N 63	4 0	110	0	8 %	+	2 abortions
					3 rs								
					1 0 130	2							
210	47 [illegible]	34	M	2 y	2 130	3	U N 13 (3 mo)	0	00	0	8 gm		1 1 7 2 gm Ca 10 mg
						)	U N 3 0						
211	43 1800	34	F	10 mo +	202 144	1	U N 0 (8 mo)	4 0	145	0	34%	+	
							U N 191						
212	23 267	7	F	9 mo	140 90		PSP 0	3	13	2			2 abo s 2 r ll hs (1 w h toxemias)
213	23 93	3	M	4 rs	142 100	1	U N 120	00	173		38%		
					4 yrs								
					2 132	0	PSP 0						
214	36-231	35	F		1 0	0	U N 1 9	3 0	200	1	67%	+	
215	38 14 7	35	F	2 rs	2 0 1 0	0	U N 83	345	1 5	3	49%		
216	43 [illegible]	36	M	9 o	1 116	1	U N 2 0	00	245			+	Cholesterol 246 mg Ca 11 mg P 15 mg
217	4 -819	33	M	5 rs	174 190	0	U N 1 6	340	170		67%	—	Ca 5 mg
							PSP						
218	38-44	36	M	6 mo	24 1	3	U N 134	632	1 7	0	41%	+	1 1 7 1 gm
							PSP 0						
219	31 11	37	F	3 5 s	158 98 (3 yrs)	0	U N 110	3 0	140	0	74%	+	
					0		PSP 7						
220	8 34	37	M	1 yr	16 130	0	U N 132	4 0	0	1	64%	+	Casts 3
						2	P 1 0						
221	35 310	37	F	7 rs	75 100	1	U N 31 (2 yrs)	44	15	1	4 %	+	
							U N 1 1						
222	7 120	37	M	4 yrs	134 9 (4 yrs)	0	U N 37 (3 mo)	842	164	0	34%		
					1 0	2							
223	41 21 4	37	M	18 rs +	2 1	0	U N 5 214	683	145	3	9%		
224	43 2	37	M	6 n	1 8 1 0	(	U N 332 (15)	4	3	1	9 5 gm		Th loss of n ter les Ca 7 4 g
225	41 1149	38	M	1 yr	170 70	0	U N 1 8	140	9	(	48%		
226	48 404	9	M	18 rs	176 0	0	U N 18	4 0	14	0	40%	—	Recurrences Ar olonel ross
227	33 1547	39	F	2 yrs	146	0	U N 5	440	1		—	—	
							PSP 0						
228	44 1 8	3	M	0 wks	1 130	(	U N 191		140	1			Casts 4
229	17 22	39	M	6 yrs	20	1		00	95	1			Th ro n os s f a t r les

TABLE 24 — SUBGROUP 4 CHRONIC AZOTEMIC GLOMERULONEPHRITIS WITHOUT HISTORY OF AN ACUTE ATTACK IN WHICH THE COMBINED WEIGHT OF THE KIDNEYS WAS LESS THAN 300 GRAMS (*Continued*)

Serial No	Autopsy No	Age	Sex	Duration of symptoms	Blood pressure mm Hg	Edema	Renal function	Weight of heart, gm	Weight of kidneys gm	Passive congestion of liver	Hemoglobin % or gm	Ret mits	Comment
230	28 347	39	F		—	1	U N 37 (6 mo)	370	226	1	55%	—	
231	37 1200	40	M		—	0	NPN 132	300	60	0	—	—	
232	41 1107	40	M	Indefinite	210/130	0	U N 82	415	210	0	67%	—	
233	41 1003	40	M	4 yrs	240/150	2	U N 155	520	140	—	44%	—	
234	33 404	41	M	7 yrs +	154/96	1—	U N 130	455	130	0	51%	0	
235	30 1631	41	M	3 yrs	170/80 220/150	0	PSP 0 NPN 90 (8 mo)	?0	210	—	—	+	
236	21 434	41	F	1 yr	180/70	2 1	U N 238	560	150	1—	—	+	
237	23 604	41	F	7 mo	210/140	3 1	PSP 0 U N 196	385	110	1—	48%	+	
238	41 1547	41	F	16 yrs +	160/100 (11 yrs) 150/90	0	U N 39 (9 yrs)	230	74	0	45%	—	Eclampsia at age 22 yrs 2 abortions 1 living child
239	41 1574	41	M	Many yrs	—	0	U N 124 NPN 99	425	340	0	63%	+	Fresh crescents
240	46 30	41	F	21 yrs	230/110	0	U N 88	400	70	0	50%	—	Toxemia of pregnancy (7 yrs) P P 54 gm
241	38 2312	42	M	—	120/70 (1 yr)	0	U N 70 (3 mo)	575	120	1	54%	—	Aortic stenosis
242	43 1576	43	F	1 wk	184/118	0	—	450	80	0	—	—	
243	42 956	43	F	5 yrs	180/118	1	U N 116	370	200	—	—	—	
244	40 218	43	F	2.5 mo	210/110	0	U N 83 156	365	(R)20 (L)80	0	40%	+	P P 6 2 gm
245	42 950	43	F	5 yrs	180/118	1	U N 170	370	200	0	53%	—	
246	46 877	43	M	10 mo	190/110	2	U N 207 cr 12	195	140	0	40%	—	
247	11 76	44	F	15 yrs	170/?	2	—	492	260	2	50%	+	5 normal pregnancies
248	21 11	44	F	21 yrs	—	0	U N 92	440	102	—	27%	—	2 toxemic pregnancies 3 abortions
249	44 425	44	M	5 yrs +	125/75 140/80	2 1	PSP 0 U N 141	300	90	0	53%	—	P P 4 6 gm
250	45 1015	44	M	3 mo	180/96	0 0	U N 186	400	230	0	40%	—	Fresh crescents
251	48 1399	44	M	2 yrs	140/90	0	U N 225 cr 13 8	440	147	0	—	—	P P 6 8 gm

252	43 962	45	M	3 yrs	175/120	0	U N 168 PSP 0	495	245	0	41%	+	P P 5 1 gm
253	47 589	45	F	6 mo	192/120	1	U N 140	420	165	0	10 gm	+	P P 6 2 gm Cholesterol 200 mg
254	33 933	45	M	1 yr +	160 120 192 140	0	U N 90 245	380	200	1−	46%	+	
255	22 619	46	F	9 wks	120 88	2 0	U N 56 PSP 10	380	165	0	44%	−	4 abortions
256	17 207	46	F	11 yrs +	160 110	0 2	U N 83 PSP 0	400	170	—	50%	—	Exacerbations
257	38-2120	46	M	1 yr +	200 120	1 2	U N 224 PSP 2	466	235	0	60%	+	P P 5 5 gm Ca 8 mg P 9 6 mg
258	38 2473	46	M	—	144 80	0	U N 70	400	153	1	32%		Fracture of leg
259	41 41	47	F	6 yrs +	110 60 (6 yrs) 170 100	1	U N 62	400	200	0	—	+	Hydrothorax fresh crescents
260	42 700	47	M	1 mo	110 60	0	U N 290	—	240	0	45%	—	
261	9 1369	47	M	5 yrs	110/70 (12 yrs)	0	U N 122	355	140	0	45%	—	
262	41 451	47	F	6 yrs +	110 60 (6 yrs) 175 100	2	U N 54 (11 da)	400	200	0	40%	+	P P 4 1 gm
263	35 1770	48	M		High	0	U N 48 (3 wks)	400	250	1	—	+	
264	36 715	49	M	1 yr	—	0	NPN 130 PSP 0	510	110	3	38%	—	
265	34 62	49	F	6 mo	210 130	3	NPN 117 PSP 12	500	290	0	—	+	
266	40 775	49	M	20 yrs	138/92	2	U N 57	500	110	1	75%	0	Unilateral fused kidneys P P 5 gm
267	41 2702	50	M	—	150 100	0	U N 14?	375	195	0	low	—	Old crescents 4
268	19 94	50	M	6 yrs	168 124	1		640	205		75%		
269	22 23	50	M	10 yrs	224 130	1	U N 95 PSP 4	440	180	—	38%	+	
270	40 745	50	F	1 yr	102 80	1	U N 112	600	92	—	38%	—	P P 5 1 gm
271	42 504	51	M	2 mo +	136 84	0	U N 36	500	135	0			Severe edema of the lungs
272	45 73	51	F	37 yrs	230 120	2 0	U N 226 cr 13 9	5.0	1.0	1−	6 gm	0	10 pregnancies Toxemia in first third and seventh P P 6 5 gm
273	45-387	52	M	7 yrs +	220/112	1	U N 128	500	28	1	8 5 gm	+	P P 4 5 gm Ca 4 6 mg P 9 7 mg
274	43 098	53	F	Many yrs	210 104	0	U N 148 cr 12	420	70		46%	—	
275	39-1449	53	F	6 yrs +	234/150	0	U N 153	340	240	0	42%	—	Toxemia of pregnancy at age 47 yrs leukemia
276	46-1949	54	F	2 mo	142 80	0	U N 145	[illegible]	250	3	30%	—	Exacerbation of subacute type
277	46-2218	55	M	14 yrs	154 94 224 156	1 0	U N 50 300	575	1180	0	63%	+	Right kidney removed (14 yrs) P P 4 4 gm
278	32 1000	55	F		134/74 (1 wk)	1−	U N 111	250	165	0	42%	+	2 abortions Cancer of stomach
279	35-1187	55	M	15 yrs	190 120	0	U N 93	590	110	0	—		
280	43 682	55	M	2 yrs	190/100	1	U N 134	4 6	184	—	36%		
281	36 2119	58	F	—	185/90	0	U N 131	350	250	1	—	+	

TABLE 24 *—SUBACUTE & CHRONIC AZOTEMIC GLOMERULONEPHRITIS WITHOUT HISTORY OF AN ACUTE ATTACK IN WHICH THE COMBINED WEIGHT OF THE KIDNEYS WAS LESS THAN 300 GRAMS (*Continued*)

Serial No	Autopsy No	Age	Sex	Duration of symptoms	Blood pressure mm Hg	Edema	Renal function	Weight of heart gm	Weight of kidneys gm	Passive congestion liver	Hemoglobin % or gm	Retinitis	Comment
282	26 4[illegible]	70	M	5 mo	180/100	—	NPN 0	400	185	0	28%	—	
283	17 112	37	M	3 yrs +	220/?	0	U N 90	575	190	1	—	—	
284	40 1307	57	M	1 yr +	190/120	0	U N 103	400	200	0	—	—	
285	41 1787	7	M	6 mo	140/95	0	U N 238	414	210	0	35%	—	
286	41 2160	57	F			0	cr 9 4	260	155	0	—	—	Ca 9 3 mg
287	49 1235	58	F	2 mo	190/110	1	U N 110	200	280	0	7 5 gm	+	Eclampsia (11 yrs) No hypertension till last 2 months
288	41 2518	60	M	0 mo +	120/80 130/110	2	cr 13 U N 127	510	235	0	32%	—	Arteriolosclerosis P P 8 4 gm
289	36 552	60	M	3 mo	140/70 (3 mo)	0	cr 11 5 U N 38 (6 wks)	495	280	3	—	0	
290	33 1018	60	M	4 yrs	—	2	U N 142	470	217	0	—	—	
291	33 552	60	M	3 5 mo	140/70	0	U N 38 (6 wks)	405	280	0	65%	—	
292	47 1618	61	M	3 mo	222/120	1	U N 22 (5 mo)	400	210	0	72%	+	
293	47 2581	62	M	1 yr	178/96	0 1	U N 182	Large	150	0	45%	+	P P 6 2 gm
294	30 473	62	M	1 yr	104 110	1	cr 14 U N 82 183	450	200	0	—	—	
295	40 1420	62	M	1 5 yrs	176 100	0	U N 127	400	155	0	—	—	
296	45 2312	63	M	6 mo +	110 70	2	U N 167	360	212	0	100%	—	Salicylate on (1 1) mild chronic P P 7 gm
297	47 1467	65	M	1 5 yrs	170/104	0	U N 102 cr 10	365	235	0	—	—	
298	37 2311	65	M	1 yr	170/100	0	—	550	190	0	31%	—	
299	30 290	65	M	2 yrs	130/82	0	U N 73, 107 (9 da) NPN 10 (9 da)	600	250	0	58%	—	
300	48 2711	69	F	6 yrs	130 70	1	U N 48	350	220	0	42%	—	Severe edema of lungs fresh crescents 4
301	45 430	70	F		130 80								
302	13 3[illegible]	70	M	1 yr	240 130	3	U N 47	400	225	0	—	—	P P 5 2 gm
303	21 437	71	M	1 yr	—	0	—	648	233	—	—	—	
304	40 1672	72	M		192 64	1	—	625	210	—	—	—	
305	40 434	75	F	8 yrs	Low	2	U N 94	700	115	—	—	—	Old valve defect
306	22 72	76	M	15 yrs	200/140	0	—	400	220	0	1 gm	—	Old crescents 4
307	40 1125	80	F	4 yrs	218 110	1	U N 62	480	240	—	52%	—	
			M	—	120 60	0	U N 110	315	170	1	—	—	Care of stomach

* Abbreviations as in Table 21

nephritis was really the outcome of the original acute attack. Did these patients recover completely from the acute attack and develop chronic nephritis at some subsequent time? This question cannot be answered satisfactorily in the absence of any information about the renal status during the latent period, but the large size of the heart and the contracted kidneys indicate a chronic nephritis of long duration. Apparently no case has been published in which a patient recovered completely from acute nephritis and subsequently developed the chronic form. We are accustomed to regard acute attacks as exacerbations of preexistent lesions when we know that the patient once had acute nephritis.

The other data on this group will be discussed subsequently.

GROUP B. *Chronic Azotemic Glomerulonephritis With No History of an Acute Attack.* — This group is four times as large as Group A in our autopsy records: there are 54 cases with history of an acute attack and 213 in which the time and manner of onset could not be determined. It is probable that some cases are in this group because of an inadequate clinical history, but it is believed that this is not a large source of error.

There is some discussion in the literature as to whether this form of nephritis is basically different from the type in which there is a history of an acute attack. It has been suggested that the form with indefinite onset never passes through an acute stage, but these cases show old epithelial crescents and remnants of polymorphonuclear leukocytes in the capillaries which are evidences of a former acute phase. There are no histological differences between those with and those without a history of acute nephritis, and we may believe that the acute attack which leads to chronic nephritis is frequently of such mild character that it is overlooked or forgotten by the patient. Inasmuch as edema is the chief clinical sign by which acute nephritis is recognized, we may believe that in the cases with insidious onset the acute attack was not accompanied by edema and was therefore not recognized as such.

For purposes of study Group B was divided into Subgroup 3, in which the combined weight of the kidneys was 300 gm. or more, and Subgroup 4, in which the weight was less than 300 gm. (Tables 23 and 24).

The entire group of chronic azotemic glomerulonephritis (Nos. 41 to 307) will now be discussed as a whole.

Age. The ages at death are shown in Table 25. It will be noted that about 40 per cent of the patients died before the age of thirty years and 78 per cent before the age of fifty years. The exact age of onset is known in only 54 of the chronic cases (Tables 21, 22). It *appears that the age of onset was the first decade in 15*, the second in 24, the third in 9, the fourth in 3, and the fifth in 3 cases. This corresponds fairly well with the time of onset of acute and subacute glomerulonephritis and lends support to the view that in the chronic

cases without history of an acute attack the actual onset of the dis-

known only in the 54 cases listed in Tables 21 and 22 In this group the total duration *from the acute attack until death was one to two* years 5 two to five years 12 five to ten years 13 ten to fifteen years 6 fifteen to twenty years 6, twenty to thirty years 5 thirty *to forty years 5 forty four years 1 and indeterminate 1* The range is one to forty four years

In subgroups 3 and 4 the duration indicated in the tables is usually only the active chronic period in which the symptoms were sufficiently severe to attract the patient s attention but in a few cases the disease was recognized at routine examination by the finding of albuminuria or hypertension before the appearance of clinical symptoms The duration of clinical symptoms was as follows one to three months 17 three to six months 17 six months to one year 23 one to two years 24 two to five years 39, five to ten years 35 ten to fifteen years 11 fifteen to twenty years 8 twenty to twenty five years 4 thirty seven years 1 *and indeterminate 34 cases.*

Frehse in a study of 248 cases of nephritis found that 68 lasted over five years 23 over ten years 19 over fifteen years 6 over *twenty years and 3 over forty years*

The Acute Attack —In the 54 cases in which there is a history of an acute attack it was in most instances typical and fairly severe confining the patient to bed for a number of weeks but in some cases it was mild and characterized only by headache with albuminuria and edema In the absence of edema mild acute cases may not be recognized The initial infections preceding the acute attack are the same as those found in acute glomerulonephritis that terminates fatally in the acute stage (Table 10)

Clinical Features The symptoms in chronic glomerulonephritis

for life insurance or for employment In such mild cases the patient has no subjective symptoms Among the early symptoms are polyuria and nocturia which are due to the inability of the kidneys to form a concentrated urine When definite renal insufficiency has developed the patient may complain of headache fatigability weakness epistaxis anorexia These symptoms are due to re[illegible] in part to the anemia resul[illegible] Disturbances of vision are due either to edema of the retina or to retinal hemorrhages

Exacerbations in Chronic Glomerulonephritis —In most instances

active chronic glomerulonephritis runs a continuous slowly-progressive course for months or years without sharp accentuation of symptoms but sometimes the clinical course is characterized by acute exacerbations and remissions. Mann in 1895 gave an excellent description of a case of twenty-eight years duration with many exacerbations related to upper respiratory infections. There was a progressive decline of renal function. Aufrecht's patient lived twenty years and exhibited many exacerbations following throat infections.

Seegal and associates in 68 patients with chronic glomerulonephritis found 13 with one or more exacerbations. Six patients had only one exacerbation and 7 developed from two to five. In all instances the exacerbations were caused by hemolytic streptococcic infections. The usual effect on the kidney was a transient decrease of renal function. The clinical evidence of an exacerbation is an increase of hematuria, albuminuria or edema.

There is a clinical record of one or more acute exacerbations in 17 of our 208 chronic cases. This low incidence may be due in part to incomplete clinical study since there was microscopic evidence of a terminal acute exacerbation in 20 cases with no corresponding clinical exacerbation. In 5 of the cases with clinical exacerbations there were no corresponding changes microscopically, probably because the exacerbations occurred too long before death—acute lesions soon pass over into the chronic form. A terminal acute exacerbation is indicated microscopically by fresh epithelial crescents, by numerous thrombosed arterioles, or by diffuse acute glomerulitis in the persisting glomeruli. It appears probable that chronic glomerulonephritis progresses toward uremia because of repeated acute exacerbations, many of which are not recognized clinically.

The glomeruli do not contract like the scar tissue of a heart valve but tend to retain the same degree of permeability that they have at the end of the acute process. Only fresh endothelial proliferation or crescent formation will produce more narrowing. The histological evidence supports the view that recurrent streptococcic infections are the cause of the progressive decrease of renal function. Since there is a similar widespread obstruction of the glomerular circulation in the terminal stages of all cases one may explain the variable duration of different cases on the degree of the initial injury and the frequency and severity of reinfections, but it is admittedly difficult to secure clinical evidence of reinfection in the majority.

Albuminuria.—Albuminuria is always present in the active chronic stage but it is usually not severe except during exacerbations and there is sometimes only a trace. Since albumin can pass

sediment but the number is not impressive except during exacerbations A definite hematuria is satisfactory evidence of an exacerbation

Edema —It is obviously impossible to give a true picture of the degree and duration of edema by means of a summarizing table The numerals in the tables give only a rough estimate of the degree of edema during the period of observation Edema is usually much more marked during acute exacerbations and it varies greatly at short intervals from time to time during the active chronic stage At times it may be very pronounced but it was continuously severe *in only 3 cases (Nos 42 57 104) In No 134 there were intermittent* attacks of severe edema Hydrothorax and ascites may occasionally be very severe even when subcutaneous edema is not prominent In No 55 death was attributed to bilateral hydrothorax and in No 300 to massive edema of the lungs *In a majority* of the cases however edema was not severe enough to demand special therapy

Edema was absent at all times during the period of observation in 105 of the 268 chronic cases (nearly 40 per cent), and it was known to have disappeared from time to time in 38 others It is often present early in the disease and absent later but the reverse also obtains

The development of edema in chronic glomerulonephritis is a complex phenomenon One of the important factors is the level of the plasma proteins Reports in the literature indicate that a moderate reduction of ' decrease is much less tha ... ins were determined in or ... gree was present in all of the 9 cases with a total plasma protein below 5 gm per cent *in 8 of 13 with protein from 5 to 6 gm in 12 of 17 with* protein from 6 to 7 gm and in 4 of 10 with protein above 7 gm per cent There is therefore not a close correlation between plasma proteins and edema

Many writers stress cardiac failure as a cause of edema The best ... the ... In ... is no ... arly ... severe congestion (2 and 3) in 19 cases Grades 2 and 3 are such as one finds in typical cardiac deaths from valvular disease and primary hypertension

absence of definite passive congestion of the liver [illegible] is clear therefore that cardiac failure is not responsible for the edema in these instances In 31 cases edema and passive congestion were associated and cardiac failure may have been a contributory or a major cause of the edema In a few cases a relationship between

cardiac failure and edema is strongly suggested by the presence of severe passive congestion of the liver

Fifteen of 44 cases with mild and four of 19 with severe passive congestion of the liver showed no edema. Edema is occasionally found when the plasma proteins are normal and the liver shows no passive congestion. Edema is not completely explained by low plasma proteins and cardiac failure. Cardiac failure is seldom a factor of major importance in the formation of edema in chronic glomerulonephritis.

Anemia.—Anemia of severe degree is present in the terminal stages in the great majority of cases. It is largely responsible for the weakness, fatigability and dyspnea on exertion. The degree of anemia is closely related to the degree and duration of renal insufficiency. Repeated determinations of hemoglobulin over a period of months or years show a slow decrease or a stationary level until the blood urea nitrogen reaches 40 to 50 mg. per cent, after which time there is usually a rapid decrease. During severe renal insufficiency there is a sharp reduction in the formation of both hemoglobin and erythrocytes. The anemia is usually of normochromic normocytic type.

Blood Pressure.—In the tables the maximum blood pressure was recorded unless it was inconsistent with other readings. Unless stated otherwise the pressure recorded was taken during the last two weeks of life, but before the onset of circulatory collapse. The time prior to death when the determination was made is frequently recorded so that the reader may judge its value. In 239 cases in which the blood pressure was recorded the maximum systolic pressures are as follows: below 120 mm. Hg, 3; 120 to 129, 6; 130 to 139, 11; 140 to 149, 20; 150 to 169, 32; 170 to 199, 90; 200 to 219, 32; 220 to 239, 31; 240 to 259, 9; and 260 to 278, 5 cases. In 3 cases the blood pressure was noted as "high," and in 2[illegible] cases there is no record.

There are 3 cases with pressures below 120 mm. Hg. In No. 2[illegible]1 the observation was made 12 hours before death, and in both Nos. 261 and 29[illegible] the weights of the hearts suggest that the pressure had been higher.

Six patients had pressures from 120 to 129 mm. Hg. No. 177 was a dwarf, and in No. 241 the pressure was taken one year before death. In Nos. 97, 25[illegible] and 307 the cardiac weights suggest a higher level of pressure.

Among the 11 persons with pressures from 130 to 139 mm. Hg there are 7 in which the heart weighed 500 gm. or more, and four of them had high diastolic pressures. These persons must have had hypertension previously. In No. 43 a pressure of 132/9[illegible] in a boy 13 years of age represents hypertension.

There are 20 cases with systolic pressures in the border zone, 140 to 149 mm. Hg. Seventeen of these may be regarded as definite hyper-

exclude hypertension

The number with systolic pressures of 200 mm Hg or higher is surprising—31 per cent of 243 cases This is conclusive evidence that a systolic pressure of 200 mm Hg or higher is not evidence against chronic glomerulonephritis and in favor of primary hypertension as is sometimes stated

phenomenon is in striking contrast to primary hypertension in which very high levels of blood pressure are usually attained early in the disease

The Weight of the Heart The weight of the heart was recorded in 256 of the 268 cases (Table 25) The 7 cases with a cardiac weight of less than 200 gm were children It will be noted in Table 25 that 80 per cent of the male hearts weighed 400 gm or more and 48 per cent 500 gm or more In the females 37 per cent weighed 400 gm or more and 8 per cent 500 gm or more In normal adult males the heart weight ranges between 300 and 400 gm in normal adult females the range is between 250 and 350 gm The normal heart averages about 50 gm heavier in males than in females but in chronic glomerulonephritis the difference is more pronounced averaging about 100 gm

In males with chronic glomerulonephritis the percentage with hearts weighing 600 gm or more is much greater in those over 30 years of age (Table 26) This may be due to a longer duration of the disease in the older individuals but it cannot be proved from the

TABLE 25—WEIGHT OF THE HEART IN CHRONIC GLOMERULONEPHRITIS

	Males	Females
Number of Cases	169	87
Below 200 gm per cent	3	2 3
200 to 299 gm per cent	2	10 3
300 to 399 gm per cent	1	45 0
400 to 499 gm per cent	32	31 3
500 to 599 gm per cent	31	8 0
600 to 849 gm per cent	17	1 1

TABLE 26 RELATION OF AGE TO THE WEIGHT OF THE HEART IN MALES WITH CHRONIC GLOMERULONEPHRITIS

Age yrs	No of Cases	400 gm + %	500 gm + %	600 gm + %
10–20	16	50	12 5	0
20–30	46	80	43	4
30–40	33	94	70	33
40–50	27	81	41	15
50–80	41	85	29	27

required of the left ventricle must depend upon the constancy as well as the degree of hypertension and the length of time involved. It often happens that the blood pressure is only moderately elevated for a number of years and becomes very high only in the terminal stages.

TABLE 27. RELATION OF THE WEIGHT OF THE KIDNEYS TO THE WEIGHT OF THE HEART IN MALES WITH CHRONIC GLOMERULONEPHRITIS

Weight of Kidneys, gm	No. of Cases	Weight of Heart, gm: 400 gm + %	500 gm + %	600 gm + %
Below 100 gm	16	50	25	12.5
100 to 199 gm	61	88	54	16
200 to 299 gm	44	91	50	20
300 to 399 gm	26	88	54	13
400 to 532 gm	11	8	54	18

One might expect to find an inverse relation between the weight of the kidneys and the weight of the heart, but when the kidneys are arranged with respect to size (Table 27), excluding persons less than fourteen years of age, *it is found that the weights of the hearts are about the same in each group.* There is therefore no relation between the weight of the heart and the weight of the kidneys.

In striking contrast with primary hypertension there were only two cases of apoplexy and there were no instances of coronary disease.

Renal Function.—Blood urea nitrogen. In the tables the time prior to death twelve observations ranged from 17 to 77 mg. per cent with 10 above 27 mg. per cent.

There are sixteen determinations from 2 months to 1 year before death. The range is from 16 to 184, with 11 above 36 mg. per cent. From 2 weeks to 2 months before death there are 24 observations ranging from 30 to 248, with 19 above 40 mg. per cent.

During the terminal stages, usually during the last week, there are 175 observations. The range was from 30 to 333, with about 75 per cent above 100 mg. per cent. In only 6 instances was the urea nitrogen less than 50 mg. per cent, and some of these patients had other diseases in addition to chronic nephritis. A very striking increase often occurs during the last few days of life. After the blood urea nitrogen has reached a level of 100 mg. per cent the patient seldom survives more than a few weeks unless the elevation was due to an acute exacerbation. After an exacerbation has subsided the urea may return to its previous level. Wakefield and Keith reported a patient with a blood urea of 200 mg. per cent and a phenolsulphonephthalein output of 0 who recovered and was working in comfort one year later.

It is not necessary to determine both urea nitrogen and non protein nitrogen According to Tileston and Comfort urea nitrogen constitutes 32 to 85 per cent of the total non protein nitrogen in disease being usually about 70 per cent

The phenolsulphonephthalein test gives about the same information as the determination of blood urea nitrogen The two-hour excretion of the dye is usually 0 during the last few weeks of life

results According to Van Slyke and his associates the urea clearance test is more delicate than any of those enumerated above but this test was seldom used in our cases

Retinitis —Retinitis in the sense of papilledema retinal hemorrhages or retinal exudates was present in 70 of the 89 patients in whom the eyegrounds were examined Nine others with very poor terminal vision are also classified as retinitis The results are shown

resent in those with

that retinitis is a

urs in chronic glo-

merulonephritis as well as in primary hypertension when the blood pressure is very high

TABLE 28 THE RELATION BETWEEN RETINITIS AND THE LEVEL OF THE SYSTOLIC BLOOD PRESSURE

Blood pressure systol mm Hg	No of Cases	Retinitis +	Retinitis 0
130 to 149	9	3	6
150 to 169	8	4	4
170 to 199	38	33	5
200+	43	39	4

The Relation Between the Size of the Kidneys and the Clinical Features —For purposes of comparison the cases without history of acute onset have been arranged in two groups *viz* those with kidneys weighing 300 mg or more (Table 23) and those with kidneys showing varying degrees of contraction and weighing from 50 to 300 mg (Table 24) The weights of the kidneys in the group with acute onset (Tables 21 and 22) are also included It appears from these tables that it is not possible to predict the size of the kidneys in chronic azotemic glomerulonephritis from a study of the clinical history One might expect that the cases of longer duration would show a greater degree of contraction of the kidneys but this relationship does not always obtain as may be seen from a study of the tables There is likewise no evident relation between the degrees of contraction of the kidneys and the level of the blood pressure It was pointed out above that there is no relation between the weight of the heart and the weight of the kidneys

In the azotemic group in which uremia was always present terminally it may seem remarkable that uremia should develop in

some instances when the kidneys are still of normal size and in others not until their weight is less than 100 gm but these differences are explainable on the basis of the histological structure of the kidneys

per cent 100 to 199 gm 43.9 per cent 200 to 299 gm 24.4 per cent 300 to 399 gm 6 per cent over 400 gm 1.2 per cent The kidneys in males are definitely larger than those in females

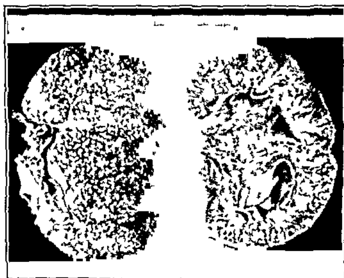


Fig 38 Chronic azotemic glomerulonephritis Contracted kidneys Photograph

The capsule is always adherent to the underlying cortex but it is much more firmly adherent in the small kidneys than in the large ones

Capsular adhesions are apparently caused by the contraction of scar tissue which *accompanies cortical atrophy* since they correspond with the atrophic depressed areas on the surface The external surfaces of contracted kidneys have a granular appearance (Fig 38) due to innumerable small pits or depressions The elevated areas or granules represent persistent cortical tissue the depressions correspond with the atrophic areas

On midsagittal section the most striking feature is the thinning

of the cortex The cortico-medullary boundaries are indistinct and usually the cortex has a faint yellowish color When a definite yellowish color is seen it is reasonably sure that we are dealing with chronic glomerulonephritis and not with primary hypertension.

The Histological Changes in the Kidneys —The variations in the size of the kidneys in the terminal stages are related to the structural changes that have taken place With respect to the size of the kidneys three groups may be roughly separated

(*a*) *Severely Contracted Kidneys* —When the combined weight of the kidneys is less than 200 gm they show a high degree of atrophy and present a fairly uniform microscopic appearance A large majority of the glomeruli are hyaline and the tubules associated with

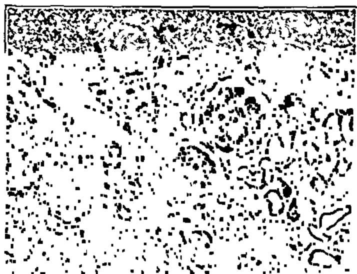


FIG 39 —Chronic azotemic glomerulonephritis Contracted kidneys The great majority of the glomeruli are hyaline All the tubules show extreme atrophy except those associated with the glomerulus that is not completely obstructed

a very few are normal with normal-sized or hypertrophic tubules, but the great majority are partially obstructed and their associated tubules show varying degrees of atrophy (Fig 39) Under higher magnification (Figs 40 and 43) the glomerular lobulation is very distinct and there is a great increase of endothelial nuclei The

capillaries in the lobules are narrowed by endothelial cells and central hyaline masses and are often displaced to the periphery of the lobule (Plate IV [upper]). In some glomeruli there is still a fair capillary permeability, in others nearly all the capillaries are completely occluded (Fig 40). The detailed structure of a persistent damaged glomerulus is shown in Plate IV. In this photomicrograph the central hyaline masses and the peripheral circulation are well shown. Chronic glomerulonephritis is readily distinguished microscopically from primary hypertension with uremia by the structure of the persistent glomeruli.

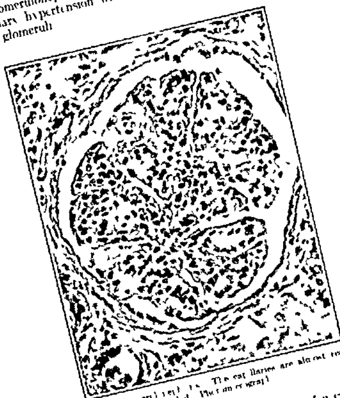


Fig 40. Chronic glomerulonephritis. The capillaries are almost completely occluded. Photomicrograph.

Fresh epithelial crescents (Fig 41) are found in a few cases. These are evidence of a recent acute exacerbation. Within a few months a fresh crescent becomes converted into dense collagenous tissue (Fig 42). The collagenous fibers are of epithelial origin; the crescent is not invaded by fibroblasts. Old fibrous crescents are found in varying numbers in nearly one-half of the chronic cases. They are evidence either of the original acute attack or of an acute exacerbation

of the cortex The cortico-medullary boundaries are indistinct and usually the cortex has a faint yellowish color When a definite yellowish color is seen it is reasonably sure that we are dealing with chronic glomerulonephritis and not with primary hypertension

The Histological Changes in the Kidneys —The variations in the

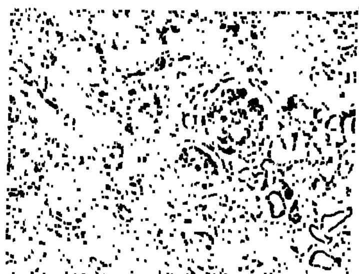


FIG 39 —Chronic azotemic glomerulonephritis Contracted kidneys The great majority of the glomeruli are hyaline All the tubules show extreme atrophy except those associated with the glomerulus that is not completely obstructed

hyaline glomeruli are either markedly atrophic or they have disap-

a very few are normal with normal-sized or hypertrophic ... but the great majority are partially obstructed and their associated tubules show varying degrees of atrophy (Fig 39) Under higher magnification (Figs 40 and 43) the glomerular lobulation is very distinct and there is a great increase of endothelial nuclei The

capillaries in the lobules are narrowed by endothelial cells and cen-

tral hyaline masses and the peripheral circulation are well shown. Chronic glomerulonephritis is readily distinguished microscopically from primary hypertension with uremia by the structure of the *persistent glomeruli*.

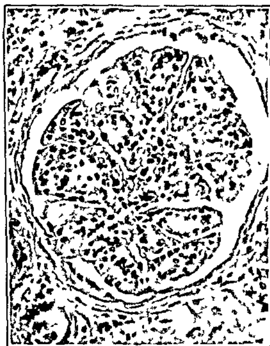


Fig. 40. Chronic glomerulonephritis. The capillaries are almost completely occluded. Photomicrograph.

Fresh epithelial crescents (Fig. 41) are found in a few cases. These are evidence of a recent acute exacerbation. Within a few months a fresh crescent becomes converted into dense collagenous tissue (Fig. 42). The collagenous fibers are of epithelial origin; the crescent is not invaded by fibroblasts. Old fibrous crescents are found in varying numbers in nearly one-half of the chronic cases. They are evidence either of the original acute attack or of an acute exacerbation

during the chronic stage When present in fair numbers they are helpful in establishing the diagnosis of chronic glomerulonephritis

(b) *Moderately Contracted Kidneys* —Kidneys with a combined weight between 200 and 300 gm resemble the group just described in all respects except that they have a larger number of persistent damaged glomeruli

(c) *Non-contracted Kidneys.*—In 10 to 15 per cent of the cases the kidneys are of normal size or even enlarged On microscopic examination it is found that hyaline forms constitute less than one-half of the glomeruli Frequently only 10 to 15 per cent of the glomeruli are hyaline, and occasionally no hyaline glomeruli are to be seen The most frequent type of nephron in these kidneys is a partially



FIG 41 —*Fresh epithelial crescent Photomicrograph*

obstructed glomerulus with moderate or severe atrophy of its tubules (Fig 43) Loose collagenous tissue occupies the space between the shrunken tubules but the kidney is not contracted There is a resemblance to subacute glomerulonephritis There are no clinical features by which these large kidneys may be distinguished from contracted kidneys

Special Histological Features —In 3 cases there were a large number of fresh thomboses in the afferent arterioles leading to the persistent glomeruli These are to be interpreted as a form of acute exacerbation and they no doubt caused acute uremia

Arteriolosclerosis —Hyaline arteriolosclerosis was found in 7 cases Hyaline changes in the arterioles are usually interpreted as an effect of the hypertension induced by glomerulonephritis, but it seems more

probable that these 7 cases represent an accidental association of chronic glomerulonephritis and primary hypertension. If the hypertension of chronic glomerulonephritis really caused arteriolosclerosis one would expect to find it more frequently than 7 times in 268 cases. Some investigators claim a much higher incidence of arteriolosclerosis in this disease but they seem not to have distinguished atrophy of arterioles from arteriolosclerosis. Disuse atrophy of arterioles is seen frequently but these vessels show no intimal disease.

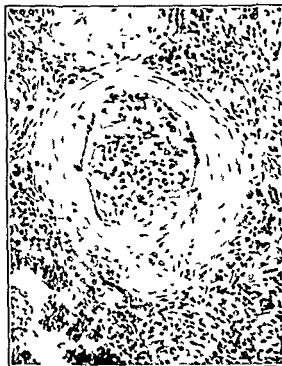


Fig. 4. Old fibrous epithelial crescent. Photomicrograph.

The Course of Pregnancy in Chronic Glomerulonephritis. When the nephritis is mild there may be no signs of toxemia other than albuminuria. Two women had 3 each and another had 5 normal pregnancies during the course of the disease. Twenty three women in this series had one or more pregnancies after the onset of the disease. Of a total of 67 pregnancies in these 23 women twenty-five proceeded normally but in the 42 others there was an exacerbation of the nephritic

symptoms producing the clinical picture of eclampsia or preeclampsia and often leading to spontaneous or induced abortion premature labor or stillbirth There were 17 spontaneous and 6 induced abortions during the first trimester There were 2 premature labors (seventh and eighth months) one spontaneous and one induced

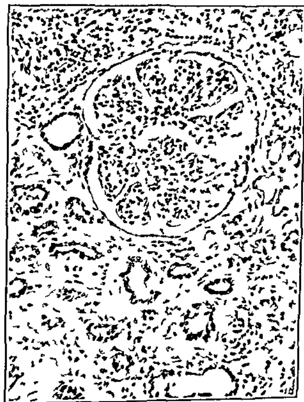


Fig 43 Chronic azotemic glomerulonephritis. Large kidneys with severe glomerular obstruction and tubular atrophy but with no hyaline glomeruli Photomicrograph

only at the first third and seventh *Usually after one abortion or* toxemic pregnancy all subsequent pregnancies are abnormal but sometimes a viable infant is born

Chronic glomerulonephritis is sometimes first recognized during

Pathological Physiology — The basic disturbance in chronic glo-

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filtrate must be correspondingly high in electrolytes Acidosis is due to retention of acid ions and to decreased formation of ammonia by the tubules

All functional tests measure the amount of functioning renal tissue that remains Surgical reduction of the renal parenchyma produces the same picture of renal insufficiency as a renal disease although in the former the remnant of renal tissue is normal

Some Principles in the Treatment of Glomerulonephritis (a) Acute Glomerulonephritis The outcome of this disease depends in large measure on the severity of the initial lesion and is not greatly influenced by therapy The physician may however be helpful when edema or cardiac failure are prominent symptoms As in other forms renal edema is treated by a low-salt low fluid diet It is never advisable to force fluids to correct an oliguria since this may lead to edema of the lungs or larynx

Addis strongly recommends a low-protein diet on the theory that it rests the kidneys It is true that the work done by the kidneys is performed by the tubules in excreting the products of protein metabolism but glomerulonephritis is a disease of the glomeruli and not of the tubules Addis treated all of his patients with a low protein diet His controls were rats with experimental renal insufficiency not persons with glomerulonephritis Pediatricians seem to obtain good results with a light balanced diet Few of them insist on a low-protein intake unless the blood urea is very high

Chronic Glomerulonephritis Therapy has very little influence in this disease except in the control of edema and cardiac failure The disease gradually progresses toward renal insufficiency because of repeated upper respiratory infections Each infection produces additional damage to the glomerular filter It is unlikely that any known therapy exerts an important influence on the progress of the diseases The patient usually comes to his physician after the onset

of renal insufficiency when very little can be accomplished therapeutically

Spontaneous Glomerulonephritis in Animals —Kirschbaum, Bell and Gordon described a spontaneous disease of female N H mice which corresponds closely histologically and clinically with human chronic glomerulonephritis The disease is characterized by albuminuria edema, nitrogen retention hypoproteinemia, anemia and hypercholesterolemia The glomeruli are partially obstructed by endothelial proliferation, but tubular atrophy does not occur

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E *Lipoid Nephrosis (Hydropic or Membranous Glomerulonephritis)* —Whether a glomerulonephritis is of the azotemic or hydropic type depends upon the character of the glomerular lesion If the

less permeable to blood and a large amount of plasma protein escapes into the urine the hydropic form results

Capillary obstruction is usually due to endothelial proliferation or to external pressure from epithelial crescents but it may be caused by extreme thickening of the capillary basement membranes

Increased capillary permeability to protein may not be associated

increased susceptibility to infection and often a decreased basal metabolic rate One may distinguish a pure form of the nephrotic syndrome in which there is little or no hypertension or renal insufficiency and a mixed form with moderate degrees of hypertension and renal insufficiency

The nephritic syndrome is characterized by hypertension and progressive renal insufficiency and edema is usually not a prominent feature

A great majority of investigators apparently believe that the nephrotic and nephritic syndromes represent distinct diseases When a case of nephrosis assumes the features of nephritis they assume that a new disease nep
and when the patient
dromes they assume th
endeavor to show that this conception is confusing and unnecessary

The nephrotic syndrome depends entirely upon a massive loss of protein in the urine which cannot take place unless the capil

about by narrowing
renal insufficiency is
caused by widespread obstruction of the glomerular capillaries When a patient with the pure nephrotic syndrome develops hypertension and uremia the usual cause is a progressive thickening of
h brings about narrowing
been introduced
nephrotic syn
drome (albuminuria edema) but in a lesser degree than in typical nephrosis

In accordance with prevailing usage we may define lipoid nephrosis clinically as a renal disease in which the outstanding feature is

TABLE 29 [illegible] A CLINICAL LIPOID NEPHROSIS OF MIXED TYPE GLOMERULAR STRUCTURE [illegible] PROLIFERATIVE GLOMERULONEPHRITIS

Serial no.	Autopsy no.	Age	Sex	Duration of symptoms	Albuminuria	Hematuria	Edema	Blood pressure	Urea nitrogen, mg per cent	Phenolsulphonphthalein, per cent	Plasma proteins	Weight of heart, gm	Weight of kidneys, gm	Hemoglobin, per cent	[illegible]	Hyaline glomeruli	Basement membranes	Endothelial proliferation	Cause of death
[illegible]	41 [illegible]	22 mo	M	8 mo	4		3 1	[illegible]	[illegible] 145		[illegible]	4				1	1	1	[illegible]
[illegible]	45 [illegible]	11	F	8	4	0	4	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]			3	1	[illegible] 481
[illegible]	47 16		F		4		4	[illegible]	130		[illegible]	[illegible]	[illegible]			1	1	3	[illegible]
311	37 [illegible]	16	F	14 mo	4	1	4	145/90 (1 yr) [illegible]	5 (1 mo)	44 (1 yr) 12 (1 wk)	4 4 1 1	408	34	46	0	1	0		[illegible]
312	34 [illegible]	21	F	9 mo	1 2	0 1	4	140/80 (4 mo)	[illegible] 4 (3 wk)	17 (2 wk)		3.8	4 2	[illegible]			0	4	3	[illegible]
313	36 [illegible]	41	M	7 yr	4	0	4	190/130		—		[illegible]	435	—	[illegible]	10	1	2	Hydrothorax
314	[illegible]	[illegible]	M	4 mo	2 4	0	3	200/115	41 6 (1 mo)			[illegible]	[illegible]			0	[illegible]	3	Lobar pneumonia

edema There is heavy albuminuria, a decrease of plasma proteins and an increase of blood cholesterol There is no gross hematuria, but some erythrocytes may be found in the urinary sediment The great majority of the cases in children and a few of those in adults show no persistent elevation of blood pressure or progressive renal insufficiency (pure type) A majority of the cases in adults and a few in children show moderate hypertension and moderate renal insufficiency (mixed form) Death usually results from peritonitis or bacteriemia, but cases of the mixed type may terminate in uremia

Lipoid nephrosis is not a sharply defined entity, it blends with

ening of the basement membranes, but some glomerular lobules or even entire glomeruli will show proliferative lesions There are also cases of nephritis with thick glomerular basement membranes in which edema is not conspicuous

Subgroup A (*Table 20*) —In this group there are 6 cases that correspond clinically to lipoid nephrosis of mixed type but belong anatomically with proliferative glomerulonephritis A representative case of this group is reported fully

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of
previous two years
On admissi
and the extre
90 mm Hg
normal Rer

to 2 mg per cent The total plasma proteins were 4 [illegible] gm per c (April, 1936), 6 27 gm (May, 1936), and 1 76 gm (February 4 1937)

The blood pressure varied from 145 90 on admission to 220 150 in November, 1936 The edema varied in intensity from time to time but [illegible] Dyspnea was usually a prominent symptom [illegible] h occurred on March 3, 1937. The

[illegible] anasarca The peritoneal cavity [illegible] the right pleural cavity 500 cc, the

left pleural cavity 800 cc, and the pericardial cavity 300 cc. There was also marked edema of the lungs. Death was apparently due chiefly to



Fig. 44. Chronic glomerulonephritis with the clinical syndrome of lipoid nephrosis of mixed type. Serial No. 311. Photomicrograph.

involved. Lobulation is distinct. The lobules show central masses of [illegible]

is no diffuse thickening of the capillary basement membranes which characterizes most cases of lipoid nephrosis.

TABLE 30—LIPOID NEPHROSIS UNDER BASEMENT MEMBRANE AND TUBULAR ATROPHY / INDICATES THAT THE INVOLVEMENT IS FOCAL AND NOT DIFFUSE AS IN THE OTHERS

Serial No.	Autopsy no.	Age yrs.	Sex	Duration of symptoms	Albuminuria	Hematuria	Edema	Blood pressure	Blood urea nitrogen mg per cent	Non-protein nitrogen mg %	Phenolsulphonphthalein %	Cholesterol mg	Plasma proteins	Weight of heart g	Weight of kidneys gm	Hemoglobin per cent	Hyaline glomeruli	Tubular atrophy	Basement membranes	Endothelial proliferation	Cause of death	Comment
315	34 387	1 5	M	6 wk	4	0	3	114/70				—			300		0	0	0	0	Streptococcic peritonitis	Onset with otitis media
316	45 [illegible]	[illegible] mo	M	6 wk	4	[illegible]	4	11[illegible]	43	—		80	A 1 8 G [illegible]	[illegible]	171	14 gm	0	0	/		[illegible] of lungs	No infection Ascites 3000 cc
317	33 1100	2	M	10 wk	4	0	4	115/ ?		60			A 1 39 G 1 52		280	87	0	0	0	1/	Peritonitis	Exacerbations
318	42 1367	2	M	1 mo	4	0	4	—	15			—	A 2 2 G 4 1	48	135	65	0	0	0	0	Pneumococcic peritonitis	Preceded by a cold
319	38 1450	3	F	3 mo	4	1	4	124 84 1 8 76	15 6 21 9			—	3	60	170		0	/	0	0	Peritonitis	Onset with common cold
320	31 656	3	F	7 mo	4	0	4	90 '50	31 5 6 mo 10 7 2 mo	—	33 2 mo	241	—	63	120	50	0	/	/	0	Pneumococcic peritonitis	Onset with sore throat
321	41 2634	3	F	4 mo	4	0	4	102/ 6	76 8	—	—	472	A 2 1 G 2 6	80	240	65	0	0	0	0	Pneumococcic peritonitis and meningitis	Intermittent edema and fever
322	39 950	3 5	M	5 mo	4	0	4	100/78 110 90	—	44	—	44	A 3 58 G 4 04 T 0 78	60	298	87	0	0	0	0	Pneumococcic peritonitis	Onset with upper respiratory infection
323	34 1 9	4	M	2 mo	4	0	1	109/70	23 8 11 6		—	258	A 2 83 G 3 09 T 0 67	80	200	90	0	0	0	0	Streptococcic peritonitis	Onset with conjunctivitis
324	28 5	4	F	1 yr	4	0	4		—		—	—		67	200	—	0	0	0	0	Bronchopneumonia	Recurrent attacks edema
325	35 461	4	M	16 mo	4	1	4 0	110 68	71 1 yr 58	—	—	251	A 1 07 G 5 97 T 0 8	75	210	92	0	0	0	0	Streptococcic peritonitis	Repeated attacks peritonitis
326	42 [illegible]	4	M	21 mo	4	1	4	96 60 1 8 70	p m 9 8	—	—	337	A 1 8 G 4 9	70	258	—	0	0	0	0	Pneumococcic peritonitis	Fat +++ Ascites 4000 cc
327	35 242	4	F	15 mo.	1 4	0	3	94 58	13 1 yr	71 1 da	—	444	A 2 0 G 2 ? T 0 8	—	250	73	0	0	0	0	Peritonitis	Onset with common cold exacerbations

279	43 1579	6	M	9 mo	1 4	0	4	96/90 110/70	10 3 1 mo	43 1 mo 27 6 3 wk	30 4 mo	713	a, 1 6 g 2 1	75	490	70	5	1f	3f	0	Streptococcic peritonitis	Onset with pneumonia
329	39 410	3	M	4 mo	4		4	122/90	15	41 9		13	4 5	43	330	90	0	0	1f	7f	Streptococcic peritonitis	Fat ++
330	44 832	5 5	M	4 mo	4		4	1[illegible] 4	79 5		20	40 3 3	a. 2 6 g. 1	1 3	735		0	0		f	?	R 100 cc pus tic fluid removed
331	40 44	8	M	8 mo	4	0	4	130 90		42		89 4 513	3 9	70	190	70	0	0	0	0	Peritonitis	Onset with pneumonia
332	76 025	6	F	6 mo	3	0	4		27 6 wk 19 1 mo		15 2 wk			60	275	65	5	0	0	0	Peritonitis	
333	33 1472	7	M	11 mo	4	0	3	96/68	11 7 9 mo 79 1 da	43 8 10 mo 73 8 1 da.	40 9 mo 74 1 mo		a 1 8 g 2 8 f 0 4		767	0	0	0	0	1	Pneumococcic peritonitis	Fat ++ recurrent
334	36 472	7	M	3 mo	4	0	2			72 3 wk		452 1175	a, 1 33 g 3 58	175	310		0	0	0	1	Erysipelas	
335	43 780	7 5	M	3 mo	4		4	114 64			35		a 1 7 g 1 5	150	4 5	12 mm	0	0	0		?	Onset with upper respiratory infect. exacerbations, few mo, 3000 cc
336	2 1 7	5	F	?	0 4	0	4	1 8 88	13 4 4 7	48 2 7 99 8 2 wk			a, 0 8 g 3 16	150	143	58	0	3	1f	1	Streptococcic peritonitis	
337	78 1 6	1	F	7 mo	3	1	4	110/50	10 3 7 mo 61 2 1 da		67 7 mo 42 1 mo			53	480	45	0	3	3	1	Streptococcic peritonitis	Crescents
338	78 820	12	F	5 mo	7	1	4	116/92				179	2 7 4 2	170	4 3		0	0	7	0	Pneumococcic peritonitis	
339	39 1301	16	M	3 5 mo	4	0	4	190/90 150/114	15 5	38		37	4 2 3 8	230	43	72	0		0	0	Streptococcic peritonitis	
340	75 101	15	F	mo	3	0		19 1[illegible]	19		70			785	335	99	0		1	0	Peritonitis	Syphilis
341	42 1 3	16	F	2 mo	3		3	116 6	26 4?				a, 1 8 g 2 1	90	49	51		3		f	Empyema pneumonia	Preceded by upper respiratory infection
342	31 1376	70	M	3 5 mo	1		3	3? 154 [illegible] 117	7 3 34 9		31	411	a, 1 4 g 1 51 f 0 40	70	400	39		2	2		Peritonitis	Bacterial endocarditis
343	70 1416	70	F	22 mo.	1 4		2 4	140/70 72 mo. 772/1-6 4 mo 1[illegible]/100 1 wk	7 7 22 mo 102 1 da 53 9 0 da	3	54 22 mo			434	4	43	1		3	0	Uremia, pneumococcic bacteremia	Followed a sore throat
344	7 50	1	M		3	0	4							3 7	349		0	1	2	0	Peritonitis	
345	33 1772	4	F	1 mo	3	0	3	194/120		57 6 2 da				550	780	48	70	3	4	1	Hydrothorax	

TABLE 30—LIPO D NEPHROSIS UNDER BASEMENT MEMBRANE AND TUBULAR ATROPHY *f* INDICATES THAT THE INVOLVEMENT IS FOCAL AND NOT D FFUSE AS IN THE OTHERS

Serial No	Autopsy n	Age yrs	Sex	Durat on of sy nptom s	Albuminur a	Hematur a	Edema	Blood pressure	Blood u ea n tr g n m per cent	Non pro e n n roge mg %	Pl n l ul h ne al %	Ch es er l	P asma pro	We ght f hea t g	We ght of k d eys gm	Hemoglobin pe cent	Hyal ne menis	Tubular a r phy	Basement mem rane	Endot el al p life at	Cause of deatl	Comment
3 5	34 383	1 5	M	6 wk	4	0	3	114 70	—				—	—	300		0	0	0	0	Streptococc c per tonit s	Onset with otitis med a
316	45 ?39	0 mo	M	6 wk	4	0	4	11	43		—	900	a 1 8 g 2 3	?	1	14 gm	0	0			Ed na of l ngs	No nfec on Asc es 3 000 cc
317	33 1100	2	M	10 wk	4	0	4	115/?	—	60		—	a 1 38 g 1 52		280	87	0	0	0	ff	Per ton t s	Exacerbat ons
318	4? 1367	2	M	1 mo	4	0	4	—	13			—	a 2 2 g 4 1	48	175	65	0	0	0	0	Pneumococc c per tonit s	*Preceded by a cold*
319	38 1459	3	F	3 mo	4	1	4	124 84 108 76	15 6 1 9	—	—		3	60	170	0	0	0	0	0	Periton tis	Onset w th common cold
3 0	31 896	3	F	7 mo	4	0	4	90 50	31 5 6 mo 0 7 2 mo	—	33 2 mo	240	—	65	190	51	0	0	0	0	Pneumococc c per ton t s	Onset w th sore throat
3?1	41 2634	3	F	4 mo	4	0	4	102 76	6 8	—	—	75	a 2 1 g 2 6	0	40	65	0	0	0	f	Pneumococc c per ton s and men ngitis	Intermittent edema and fever
3 ?	39 250	3 5	M	5 mo	4	0	4	00 76 110 90	—	44	—	447	a 3 08 g 4 04 f 0 78	6	208	87	0	0	0	0	Pneumococc c per tonit s	Onset w th upper resp ratory nfect on
323	34 179	4	M	2 mo	4	0	1	108 70	3 8 11 6		—	8	a 2 03 g 3 09 f 0 67	80	?0	90	0	0	0	0	Streptococc c per ton s	Onset with conjunctivit s
3 4	8 5	4	F	1 yr	4	0	4	—	—	—			↔	67	?00	—	0	0	0	0	Bron hopneumon a	Recurrent attacks edema
3.5	35-481	4	M	18 mo	4	1	4 0	110 68	21 1 yr 58 p m 9 8		—	1	a 1 07 g 5 97 f 0 8	75	?0	8	0	0	0	0	Streptococc c ?r per ton t s	Repeated attacks per ton s
3 6	42 ?61	4	M	21 mo	4		4	96 60 1 ? 70			—	3 7 8	a 1 8 2	0	8		0		0	0	Pneumococcic per on is	Fat +++ Asc es 4 000 cc
327	35 242	5	F	15 mo	1 4	0	3	94 68	13 1 yr	71 1 da	—	44	a 2 0 g ? 2 f 0 8	—	2?0	75	0	0	0	0	Periton tis	Onset with common co d exacerbations

C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16	C17	C18	C19	C20	C21	C22	C23
2?6	33 1579	6	M	30 mo.	1 4	0	4	96/60 110/70	10.5 1 mo.	43 1 mo. 77.6 3 wk	30 1 mo	115	a, 1.6 g 2.3	5	?90	70	5	11	31	0	Streptococcic peritonitis	Onset with pneumonia
2?9 330	39 2000 44 ? 1	4 5.5	M M	4 mo 4 mo	4 4	0 0	4 4	[illegible] 1?/?1	13 ?9.5	41.9	— 20	?15 ?? 3.3	4.3 a, 2.4 g 1	43 1.5	330 35	90	0 0	0	31 0	27 ?	Streptococcic peritonitis ?	Fat ++ 1 ?00 cc ascitic fluid removed
331	40 94	6	M	6 mo	4	0	4	130/90		42		with 513	3.9	70	190	70	0	0	0	0	Peritonitis	Onset with pneumonia
1	6 ? 5	6	F	4 mo	2	0	4		27 8 wk. 19 1 mo.		13 2 wk		—	60	2.5	65	3	0	0	0	Peritonitis	
3 3	33 11?2	7	M	13 mo	4	0	3	96/64	11.7 9 mo ?9 1 da.	43.9 10 mo 75.8 1 da.	40 9 mo 74 1 mo	—	a, 1.8 g 2.8 ? 0.4	—	?67	70	0	0	0	1	Pneumococcic peritonitis	Fat ++ recurrent
3?6	34 4?3	7	M	1 mo.	4	0	2			?? 3 wk	—	432 1.5	a, 1.33 g 3.30	1.5	310	—	0	0	0	1	Erysipelas	
333	4? ??	7.5	M	5 mo	4	0	4	118/64			53		a, 1.7 g 1.8	150	40?	12 gm.	0	0	0	0	?	Onset with upper respiratory infection; ?? ??, 400 cc
3?6	32 1??	9	F	yr	0 4	0	4 0	1?8/?4	13.4 2 yr	44 2 yr 99.8 ? wk			a, 0.8 g 3.16	140	115	50	0	0	11	1	Streptococcic peritonitis	
337	? 1 9	11	F	7 mo	3	1	4	11? ?0	10.2 7 mo 61.2 1 da.		43 7 mo 4 1 mo			1?	180	45	0	2	3	1	Streptococcic peritonitis	Crescents
3.8	30 ??0	13	F	5 mo	?	1	4	118/??			—	60.9	?.7 4.2	170	4.5	—	0	0	2	0	Pneumococcic peritonitis	
3 9	35 1301	16	M	2.5 mo	4	0	4	170/90 133/110	15.5	38		9.7	4.2 5.0	230	?8	73	0	0	0	0	Streptococcic peritonitis	
340	?5 195	35	F	7 mo	3	0	?	10? 1?0	10		?			?65	335	90	0	0	1	0	Peritonitis	Syphilis
341	? 1 5	15	F	2 mo	3	0	3	118, 8	?6 4				a, 1.8 g, ?.1	?00	4?	?0	?	0	?	?	Empyema, pneumonia	Preceded by upper respiratory infection
342	33 1 69	?0	M	5.5 mo.	4	0	3	1?4/?4 11?/112	20.3 39.0		31	471	a, 1.?5 g, 1.31 f 1.4	?30	4.0	59	0	2	?	0	Peritonitis	Bacterial endocarditis
343	?? 1?,?	20	F	?2 mo.	1 4		3 4	130/70 2 mo 227/134 4 mo.	7.7 ?2 mo. 102 1 da.		34 23 mo			454	?4	43	10	2	3	0	Uremia, pneumococcic bacteremia	Followed a sore throat
344	? ??	1	M		2	0	3	1?0/110 1 wk	53.9 9 da.					38	140		?	1	2	0	Peritonitis	
345	35 1??2	4	F	1? mo.	3	0	3	1?0/130	—	57.0 2 da.	—			5.0	??	48	?0	3	4	1	Hydrothorax	

TABLE 30—(*Continued*)

Serial No	Autopsy No	Age yrs	Sex	Duration of symptoms	Albuminuria	Hematuria	Edema	Blood pressure	Blood urea nitrogen mg per cent	Non protein nitrogen mg %	Phenolsulphonphthalein %	Cholesterol mg %	Plasma proteins gm %	Weight of heart gm	Weight of kidneys gm	Hemoglobin per cent	Hyaline glomeruli %	Tubular atrophy	Basement membranes	Endothelial proliferation	Cause of death	Comment
346	37 ?71	27	F	6 mo +	3	0	1 2	136/80	—	38 128 46	70		4 2	310	475	4?	0	0	3	1	Lobar pneumonia	Wire loops 4 began with otitis media
347	?9 1850	27	M	3 yr	3		3	160/100	9 1 mo	36 1 mo	65 1 mo	—	a 0 69 g 3 26	—		74	10	1	4	2	Peritonitis	
348	?8 647	28	M	1 mo	4	0	3	—	16 7 12 da 48 5 1 da		—	240 383	4	315	510	81	0	0	1	1	Streptococcic peritonitis	
349	3? 1080	31	M	6 yr	1 4	1	2	158/96 6 mo 236/176	28 5 mo	41 4 6 mo 166 5	65 6 mo 5	—	a 0 9 g 2 6	575	400	69	10	2	2	2	Uremia	Retinitis casts +++
350	32 1803	31	M	10 wk	4	0	3	118/80 150/78	29 8 64 8 da	—	37 3 wk	103	a 0 63 g 1 67 f 0 79	250	400	85 4?	0	0	0	2	Lobar pneumonia	Oliguria
351	34 1536	32	F	2 yr	4	0	3 0	130/98 2 yr 190/112	31 2 2 yr 120 4	—	50 2 yr 0	?30	a 1 49 g 1 09 f 0 66	440	170	44	70	3	3	0	Uremia	
352	47 2198	32	M	3 m	4	0	1	175/110 158/108	123	—	—	—	—	325	450	—	0	0	3	0	Uremia	Ascites 4500 cc
353	?8 183	34	F	7 mo	3		3 0	200/140 1 mo	47 1 wk	—	0 1 wk	—	—	300	300 one	48	0	1	2	0	Bronchopneumonia	
354	35 654	30	M	5 wk	4	0	3	108/74	—	38 2 wk	—	—	a 1 0 g 0 9 f 0 7	240	365	73	0	0	1f	1	Accident	
355	37 2146	36	M	1 yr	3	0	3	130/90 2 mo 160/120	28 7 2 mo	—	15	423	a 2 97 g 1 83 f 0 33	340	4?0	70	0	0	1	0		Otitis media
356	31 1672	37	M	16 mo +	3		3	150/90	—	—	—	—	—	325	435	—	5	0	3	2	Hydrothorax	
357	25-636	37	M	5 yr +	2	1	2 1	150/120 170/120 2 mo	31 2 mo 159 5 da	—	—	—	—	450	375	—	50	3	3	0	Uremia old crescents	
358	48-2738	37	F	18 mo	+	0	0	190/100 250/130	57	—	—	—	—	350	90	62	0	0	3	0	Uremia	Retinitis
359	41 1997	38	M	11 wk	4	0	4	170/108	46	—	—	—	a 1 9 g 2 5	345	440	80	0	0	f1	f1	Edema of lungs	40 liters of ascitic fluid removed
360	20-43	38	M	5 yr	3	0	3	1?2/84 1 mo	16 4 1 mo	—	30 1 mo	—	—	325	390	52	10	0	2	1	Pneumonia	

361	27-975	29	F	6 yr	2 1	0	2 4						—	764	767	20	0	0	2	1	Severe anemia	
362	35-945	40	M	9 mo.	3		4	13 90 8 mo. 114/74	14 8 mo.	38 4 mo.	63 8 mo.	259	a, 1 76 g, 1 64 f 0 49	323	445		0	0	3	0	Bacterial endocarditis	Followed sore throat
363	33-1127	43	M	7 yr	4	0	4	Normal to 250/?	Normal to very high					500	275		90	4	3	0	Uremia	5 years as pure type
364	17-230	45	M	1 yr		0	1 4	140/70	4 9 da.		30 1 mo.			400	360		0	2	3	0	Lobar pneumonia	Crescents
365	33-574	45	M			0	4 0	176/70 165/90 3 wk	22 3 wk	47 3 wk	65 3 wk			475	400	—	10	1–	3	1	?	
366	33 3	47	M	9 mo.	4	0	4	185/172 148/170	19 17		33 0	741	a, 2 14 g, 1 6 f 0 65			98 60	30	3	3	0	Uremia	
367	17-473	47	F	16 mo.	1 2	0	4	170/70 148/90	44 173			2.4	4 6	180	290		10	0	2	1½	Uremia	Severe recurring edema
368	31 1649	48	M	4 mo.	4	0	2 4	148/112 4 mo 162/104		77 4 mo 95 1 da.	33 4 mo			Normal	305		10	1	2	0	Inanition	
369	44-574	50	M	8 mo.	0 4	0	0 4	105/70 2 yrs 210/130	37					350	383	82	0	0	3	0	Uremia	Retinitis
370	27 3 3	52	F	2 yr	+			—	—	—	—		—	315	350	90	10	1	3	2	Perforated ulcer wire loops ++	
371	34 1953	52	M	4 mo.	4	0	3	180/108	96 1 mo	204 1 da.	0 1 mo		—	500	355	78 50	0	1	3	3	Uremia	Casts ++++ wire loops +
372	45-736	53	M	4 yrs	4	0	3 0	188/104	137 293					625	220		20	3	3	0	Uremia	
373	17 148	54	M	1 yr	2	0	4	153/90 140/95	13 10 mo 73 10 da.		72 10 mo 70 10 da.			330	440		10	1	1	1	Purulent bronchitis	
374	47 2170	55	M	6.5 yr	1	0	3 1	144/92 4 yrs 170/95	16 8 4 yr 214 p.m.		35 4 yr	333 4 yr	a, 3 3 g 3 1 4 yr	400	155	82 56	75	3	4	0	Uremia	
375	35 114	58	M	3.5 yr	3	0	3	140/90	15 9 2 wk		44 2 wk		a 1 91 g 2 62	240	270	56	0	0	3	0	Streptococcic peritonitis	
376	45-547	62	F	15 yr	3	1	3	131/82 2 da.	25 1 da.				—	330	260	40	0	0	3	0	Severe anemia	Began with an acute attack
377	45-278	63	F	7 mo			3							330	155	—	10	1	3	0		Arteriosclerosis. Died on admission
378	39-1763	63	M	7 wk	4	0	4	178/100	40 1 wk				a 0 79 g 1 55	330	340	90	0	0	2	0	?	
379	45 620	69	M	1 yr	3	0	4	134/80 170/90	14 70		30	763 556	a, 3 3 g, 1 2		234	44	0	1	3	0	Peritonitis	
380	47 1473	71	M	1 yr	4	0	2	210/1??	16 29		47	590	a 4 0 g 1 7	350	200	64	50	2	0 3	0 3	Coronary thrombosis	Majority of glomeruli normal
381	43-972	73	M	1 yr	4	0	4	180/110	27 40			183	a, 3 ? g 1 9	260	215	60	0	0	3	0		Onset after a severe cold. Ascites 3000 cc., hydrothorax 2000 cc.
382	36 433	74	F	3 mo	1	0	4						—	375	210	70	5	0	2	0	Severe anemia	

Nos 312 313 and 314 like No 311 are examples of chronic proliferative glomerulonephritis in which death occurred before the onset of renal insufficiency It may be said therefore that occasionally chronic proliferative glomerulonephritis may completely reproduce the clinical syndrome which we are accustomed to call lipoid nephrosis of the mixed type

In No 308 the clinical picture suggested pure lipoid nephrosis [illegible] *of the* [illegible] There [illegible] erminal acute exacerbation

In No 309 the disease persisted for 8 years with repeated exacerbations induced by upper respiratory infections and remissions during which the edema would largely disappear For nearly eight years the clinical features corresponded entirely to pure lipoid nephrosis except that the blood pressure was occasionally elevated, but terminally uremia developed At autopsy the kidneys showed proliferative glomerulonephritis with moderate tubular atrophy due to partial occlusion of the glo[illegible]

unlike those of typ[illegible]

small and unevenly [illegible]

[illegible] The various clinica[illegible] We shall now survey [illegible]

Frequency —It is difficult to determine the comparative frequency of the hydropic and azotemic types of chronic glomerulonephritis from the literature In our autopsy material there are 75 cases of the hydropic form and 307 of the subacute and chronic azotemic type Approximately 20 per cent of the cases of nephritis which [illegible] *id nephrosis* [illegible] ung children [illegible] ature of this disease deal with children Our autopsies show that [illegible] of 45 deaths from nephritis in children under ten years of age were from lipoid nephrosis (Table 15)

Duration of Symptoms —The duration of symptoms in our 68 cases (Table 30) is as follows less than two months 6 cases two to three months 5 three to six months 14 six months to one year 11

one year to two years 16, two to four years 7, over five years 7, and indeterminate 2. The duration is estimated from the onset of edema, but it has been observed that albuminuria precedes the edema (Rennie) and it is highly probable that a large amount of protein is lost in the urine before edema develops. The actual duration of the disease must therefore be longer than the symptoms suggest.

In general the cases of pure type have a shorter duration than the mixed form, but there are exceptions. Many cases of long duration are recorded in the literature: Davison and Wilbur, six years; Steinitz, eight years; Munk, fifteen years. In our case No. 363 the syndrome of pure lipoid nephrosis continued for five years, after which hypertension and renal insufficiency developed, the total duration being seven years.

Exacerbations and Remissions. A notable clinical feature of lipoid nephrosis is the variation in intensity of symptoms from time to time. Davison and Wilbur noted exacerbations and remissions in 50 per cent of their 20 cases, and 1 patient had 13 attacks during a period of five years. Schwarz and Kohn found peritonitis or bacteremia in some exacerbations from which the patients recovered. In 7 of our cases exacerbations and remissions were prominent, and in No. 325 there were repeated attacks of peritonitis. Sometimes a cold or a sore throat precedes the exacerbation. In the interval between attacks edema may disappear entirely and the albumin in the urine may be reduced to a small amount, but apparently it never disappears entirely. In many patients the disease runs its course without exacerbations or remissions.

Initial Infection. In acute proliferative glomerulonephritis there is usually a history of preceding infection, but in lipoid nephrosis there is no such convincing relationship. In 16 of our cases (Table 30) the appearance of edema was preceded or accompanied by an infectious process, but in the others the onset was insidious and edema or weakness was the first symptom. Many observers have commented upon the usual absence of an initial infection.

The Urine. (*a*) *Oliguria.* Oliguria is nearly always noted during the periods when edema is increasing. This is clearly due to diversion of water from the kidneys to the connective tissue and serous cavi-

sions, however, the urine may contain only small amounts of protein. The protein in the urine is chiefly albumin and this corresponds with the plasma, which shows a much greater depletion of albumin than of

globulin The walls of the glomerular capillaries are injured in such a way that they become permeable to the plasma proteins and the amount of leakage of protein is apparently unrelated to the type of structural alteration in the capillaries As much protein escapes from capillaries without visible alterations as from those with thick basement membranes but albuminuria decreases with marked narrowing of the capillaries and onset of uremia

The basic disturbance in lipoid nephrosis is a leakage of protein through the glomerular capillaries and all the features of the nephrotic syndrome are referable to loss of plasma proteins Those investigators who believe that lipoid nephrosis is not a disease of the kidney attribute the loss of protein to changes in the proteins themselves and not to a lesion of the glomerular filter This topic will be discussed later

(c) *Hematuria* —The urinary sediment usually contains only a few erythrocytes In 53 of our 59 cases in which the sediment was examined there were only a few red cells In 5 cases there was a definite microscopic hematuria and in 1 instance (No 337) there was gross hematuria An occasional writer insists that microscopic hematuria excludes lipoid nephrosis but this arbitrary limitation is now generally abandoned However a great many would not accept a c[illegible]

Murphy)

lipoid neph[illegible]

blood in on[illegible]

hematuria but otherwise the complete syndrome of nephrosis was present

It may be said therefore in the light of clinical experience that with the syndrome of nephrosis there are usually only a few erythrocytes in the urinary sediment but sometimes a large number of red cells is found and in rare instances there is gross hematuria

Edema —Edema is a necessary diagnostic feature of lipoid nephrosis although it varies in intensity from time to time and may disappear entirely during remissions It is due to depletion of the plasma proteins Often edema is the patient s most distressing symptom The anasarca produces great discomfort and the skin of the legs ma[illegible] rupture and allow the discharge of fluid

r
e

the blood pressure was no[illegible]

the course of the disease. In the 23 patients under 20 years of age 19 had normal blood pressure, 3 had a slight elevation, and 1 had definite hypertension. In the 36 patients over 20 years of age 7 had normal blood pressure and 29 had definite hypertension.

In the 30 cases with definite hypertension 26 show diffuse thickening of the capillary basement membranes, 3 show focal thickening only, and 1 shows glomerulitis with normal basement membranes. In the 26 cases with normal blood pressure, 8 show diffuse thickening of the basement membranes, 4 show only focal thickening, 4 show focal endothelial proliferation with normal membranes, and 10 show normal glomeruli. In the 3 cases with slight elevation of blood pressure there were no glomerular lesions. A

In 27 cases under twenty years of age 21 show normal basement membranes, 3 show focal and 3 show diffuse thickening. In 41 persons over twenty years of age, 36 show diffuse and 4 show focal thickening of the membranes. Only 1 had normal basement membranes. The thickening of the basement membranes is therefore more closely related to the age of the patient than to the blood pressure.

The Size of the Heart. Cardiac hypertrophy is not a prominent feature of lipoid nephrosis, although it is sometimes present in those with hypertension. In 14 females over eighteen years of age the weight of the heart was as follows: below 350 gm., 8; 350 to 450 gm., 3; and over 450 gm., 2 cases. In 25 males over eighteen years of age 16 hearts weighed less than 400 gm., 7 weighed 400 to 500 gm., and 2 over 500 gm. There were no clinical signs of cardiac failure in any case, and the livers showed no passive congestion.

Renal Function. In 13 of the cases listed in Table 30 death was due to uremia, and in 12 of these the obstruction of the glomerular capillaries by the thickened basement membranes affords an adequate anatomical explanation of the renal insufficiency. In No. 371 uremia was probably caused mainly by casts. In most of the cases with moderate nitrogen retention there is sufficient diffuse thickening of the basement membrane to interfere with renal function. Slight or transient elevations of blood urea are best explained by oliguria due to retention of water in the tissues.

Blood Cholesterol. Blood cholesterol is nearly always increased and may reach values above 1000 mg. per cent. Gottfried and associates made a thorough study of 30 young children with lipoid nephrosis. Cholesterol was always increased and ranged from 300 to 1080 mg. per cent. The total blood lipids were also increased, ranging from 1190 to 3113 mg. per cent.

Hyperlipemia occurs also in cases of chronic glomerulonephritis

that exhibit severe edema and hypoproteinemia The increase of blood lipids seems to be caused by the depletion of the plasma proteins Fishberg and Fishberg found an increase of blood cholesterol after repeated hemorrhages This occurs even in the absence of edema and the fat is withdrawn from the fat depots of the body

The Plasma Proteins —The plasma proteins are decreased in practically all cases of lipoid nephrosis and often the reduction is severe This feature is so constant that one hesitates to make the diagnosis when the plasma proteins are normal The proteins tend to increase during remissions The decrease of proteins is responsible for edema hypercholesterolemia and probably also for the increased susceptibility to infections since gamma globulin has been found to be definitely reduced Plasma albumin decreases more than globulin since its molecule is smaller and passes more readily through the

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amount of albumin than to the total protein

In No 342 the colloid osmotic pressure of the plasma was 9 cm of water and in No 366 it varied from 12 to 17 cm of water

Calcium —In non uremic lipoid nephrosis with hypoproteinemia the blood calcium is low usually around 7 mg per cent (Gottfried et al) The diffusible calcium comprises 55 to 70 per cent of the total The non-diffusible calcium is probably bound to protein and this fraction is decreased in hypoproteinemia In uremia of any form retention of phosphorus causes a decrease of calcium (Salvesen and Linder)

Hemoglobin —A moderate degree of anemia is frequently found in lipoid nephrosis Gainsborough found anemia in all of his cases In 51 of our cases in which hemoglobin was determined it was below 50 per cent in 13 cases In Nos 361 and 382 it was only 20 per cent Such an extreme reduction of hemoglobin suggests an associated primary anemia and some investigators would probably be unwilling to accept these 2 cases as examples of lipoid nephrosis I have included them because they had albuminuria and edema and exhibited the characteristic thickening of the basement membranes

The level of hemoglobin depends to some degree upon the stage of the disease when the determination is made since it often decreases progressively and is much lower in the terminal than in the early stages The anemia is of normochromic type It is more marked in association with renal insufficiency but is often severe in the absence of nitrogen retention Grossman obtained a good response to liver in one patient with severe anemia

The Kidneys The kidneys are usually but not invariably enlarged, occasionally attaining a combined weight of 450 to 500 gm

In those that die of uremia they may be somewhat decreased in size (Nos 351, 374) The external surfaces are smooth On section the cortices usually show a faint or definite yellowish color but often no yellowish tinge can be seen

Microscopic Structure —(a) *The Tubules* In those cases (Table 30) in which the glomeruli show no visible alterations the tubules are all of normal size or enlarged They never show necrosis and coarse hyaline granules are seldom conspicuous However the



Fig 43. Serial No 2[illegible] Lipoid nephrosis About 5 per cent of the glomeruli show this structure the others being normal histologically The basement membranes are very thick and the capillary lumens are largely obliterated Mallory Heidenhain stain Photomicrograph

proximal convoluted tubules usually show many fat droplets In some cases the accumulation of fat is quite marked in others only a few droplets are to be found This accumulation of fat is the only evidence of tubular disease but many writers consider this alteration sufficient evidence to establish lipoid nephrosis as a tubular disease But it is well known that many of these fatty kidneys excrete urea and phenolsulphonephthalein as well as normal organs do It is also well known that the normal kidneys of the cat contain

that exhibit severe edema and hypoproteinemia The increase of blood lipids seems to be caused by the depletion of the plasma proteins Fishberg and Fishberg found an increase of blood cholesterol after repeated hemorrhages This occurs even in the absence of edema and the fat is withdrawn from the fat depots of the body

The Plasma Proteins —The plasma proteins are decreased in practically all cases of lipoid nephrosis and often the reduction is severe This feature is so constant that one hesitates to make the diagnosis when the plasma proteins are normal The proteins tend to increase during remissions The decrease of proteins is responsible for edema hypercholesterolemia and probably also for the increased susceptibility to infections since gamma globulin has been found to be definitely reduced Plasma albumin decreases more than globulin since its molecule is smaller and passes more readily through the glomerular capillary walls Fishberg and Fishberg found that globulin is more rapidly regenerated than albumin Since the albumin molecules are smaller 1 gm per cent of albumin is equivalent in *osmotic pressure to about 3 gm per cent of globulin Therefore the* colloid osmotic pressure of the blood is related more directly to the amount of albumin than to the total protein

In No 342 the colloid osmotic pressure of the plasma was 9 cm of water and in No 366 it varied from 12 to 17 cm of water

Calcium —In non uremic lipoid nephrosis with hypoproteinemia the blood calcium is low usually around 7 mg per cent (Gottfried et al) The diffusible calcium comprises 55 to 70 per cent of the total The non-diffusible calcium is probably bound to protein and this fraction is decreased in hypoproteinemia In uremia of any form retention of phosphorus causes a decrease of calcium (Salvesen and Linder)

Hemoglobin —A moderate degree of anemia is frequently found

Such an extreme reduction of hemoglobin suggests an associated primary anemia and some investigators would probably be unwilling to accept these 2 cases as examples of lipoid nephrosis I have included them because they had albuminuria and edema and exhibited

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The Kidneys The kidneys are usually but not invariably enlarged occasionally attaining a combined weight of 450 to 500 gm

In those that die of uremia they may be somewhat decreased in size (Nos 361 374) The external surfaces are smooth On section the cortices usually show a faint or definite yellowish color, but often no yellowish tinge can be seen

Microscopic Structure (a) *The Tubules* In those cases (Table 30) in which the glomeruli show no visible alterations the tubules are all of normal size or enlarged They never show necrosis and coarse hyaline granules are seldom conspicuous However the



Fig. 45 Serial No 23 Lipoid nephrosis About [illegible] per cent of the glomeruli show this structure the others being normal histologically The basement membranes are very thick and the capillary lumens are largely obliterated Mallory Heidenhain stain [illegible] magnification

proximal convoluted tubules usually show many fat droplets In some cases the accumulation of fat is quite marked in others only a few droplets are to be found This accumulation of fat is the only evidence of tubular disease but many writers consider this alteration sufficient evidence to establish lipoid nephrosis as a tubular disease But it is well known that many of these fatty kidneys excrete urea and phenolsulphonephthalein as well as normal organs do It is also well known that the normal kidneys of the cat contain

is much fat in the tubules as is ever seen in lipoid nephrosis and he occasion lly sees human kidneys with a large amount of tubular fat but without any functional disturbance There is therefore satisfactory evidence that droplets of fat do not interfere seriously with tubular functions and it seems probable that the fat droplets in the tubules do not represent tubular injury but an absorption of

which they interpret as
studies however deal
it is this group in which the glomerular lesions are least conspicuou

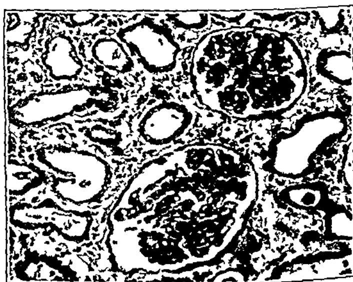
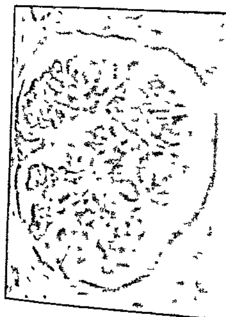


Fig 46 Lipoid nephrosis of mixed type ... Serial No 368 The capillaries show thick ... The ... Hema oxylin-eosin stain Photomicrograph

In 22 of the 68 cases the basement membranes are normal and 19 of these individuals were under ten years of age With one exception No 350 those with normal basement membranes presented the clinical picture of pure lipoid nephrosis or showed onl

Three of these were typical pure lipoid nephrosis clinic ... showed a minor variation from this syndrome and two had hypertension



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There was a diffuse thickening of the capillary basement membranes (Grades 1 to 4) in 39 cases. Six of these cases were examples of pure lipoid nephrosis and 2 others showed slight variations from the pure type. In 4 the data were insufficient to separate the two types and 27 cases were definitely of the mixed type.

Focal proliferative glomerulitis was found in 9 instances and subclinical diffuse proliferative glomerulitis was observed in 13 cases. Proliferative glomerulitis is probably the result of the same injurious agent that damages the basement membranes and not the result of an associated terminal infection as is often stated, since it is found in the absence of a terminal infection. The frequent prominence of the endothelial reaction indicates that lipoid nephrosis and proliferative glomerulonephritis are not sharply separable.



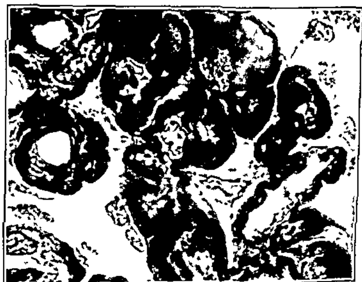
Fig. 47.—Lipoid nephrosis of mixed type. From same case as Figure 46. Mallory-Heidenhain stain. Note the thick basement membranes and narrow capillary lumens. (Photomicrograph.)

Under low magnification a lipoid nephrosis of the mixed type shows a characteristic picture (Fig. 46). Because of moderate atrophy the tubules are widely separated and the thick walls of the glomerular capillaries are easily seen. With the Mallory-Heidenhain stain the thick basement membranes are colored a deep blue (Fig. 47 and Plate III). Under very high magnification (Fig. 48) it is seen that the thickened membranes are not solid but have a somewhat porous structure.

When the thickening of the basement membranes is extreme (Grades 3 and 4) there is usually a diffuse tubular atrophy of some

degree (Fig 46) This is interpreted as disuse atrophy resulting from decreased glomerular filtration It is not a primary tubular

glomeruli are hyalinized and their tubules have undergone extreme atrophy as in glomerulonephritis (Fig 49, No 363) At first glance the appearance suggests chronic glomerulonephritis, but a careful study of many glomeruli shows that the hyaline condition is due to a progressive thickening of the basement membranes with occlusion of the capillaries



Transitions Between Membranous and Chronic Proliferative Glomerulonephritis (Table 31) —There are 4 cases in our records in which

quently mild or absent These cases lipoid nephrosis and proliferative glomerulonephritis are not sharply separable entities

The Prognosis in Lipoid Nephrosis —All cases of the mixed type ultimately die either from infection, uremia or inanition, but some

cases of the pure type recover It is difficult to determine the fre-

patient may be dismissed as cured during a remission and not seen later If we accept the clinical diagnosis made by the several reporters a number of patients recover Fanconi 8 pure nephroses, all recovered after months or years, Gainsborough 3 nephroses recovered, Evans 1 complete recovery in five months, Steinitz 1 complete recovery after eight years, non-protein nitrogen 121 mg per cent at one time, Munk 1 complete recovery after fifteen years, Eckstein 1 recovery after three years, Schreyogg 4 completely healed after one to ten years 4 others in fairly good condition but with albuminuria, Dorch 3 recoveries, Schwarz and Kohn 17 nephroses, 6 dead and none completely recovered

TABLE 31 —TRANSITIONS BETWEEN MEMBRANOUS AND CHRONIC PROLIFERATIVE GLOMERULONEPHRITIS

Serial No	Autopsy No	Age	Sex	Duration of symptoms	Albuminuria	Hematuria	Edema	Blood pressure	Blood urea nitrogen	Non protein nitrogen	Phenolsulphonephthalein	Weight of heart gm	Weight of kidneys gm	Hemoglobin	Hyaline glomeruli %	Tubular atrophy	Basement membranes	Endothelial proliferation	Old crescents	Cause of death
383	35 1292	24	F	17 mo edema 7 mo	3	0	4	194 130	—	87 6	—	550	230	43	60	4	3	0	2	Uremia
384	39 2024	49	M	4 yr +	4	1	2 0	13 /75 terminal 190/110	238 191	—	—	390	250	32	80	4	3	0	4	Uremia
385	23 203	52	M	3 yr	3	0	3	205/105 170/90	30 59		0	500	215	50	50	2	?	1f	2	?
386	26-302	60	M	1 yr	—	—	2	194 114	149	—	—	550	220	—	50	3	3	0	2	Uremia

Rennie studied 29 patients with the 'nephrotic syndrome '

dren Twenty-six were alive and 19 of these were well from one to sixteen years after onset There were 15 deaths and 10 autopsies At autopsy 4 showed no glomerular lesions 4 showed minor and 2 severe glomerular lesions

Schwarz and associates (1943) gave a report of 40 cases of lipoid nephrosis Twenty-two of the 40 patients were dead at the time of the report, and the authors had followed 8 of the survivors from seven to twenty years Some children which were regarded as cured

later developed hypertension The blood pressure was increased at some time in all 8 patients who were followed a long time One patient, now seventeen years old and observed for thirteen years had a blood pressure of 190/120 mm Hg and another now nineteen years old and under observation for seventeen years had 150/90 mm Hg

This excellent study suggests either that pure lipoid nephrosis often progresses into the mixed form if the patient survives many years, or that acute glomerulonephritis is sometimes incorrectly diagnosed as lipoid nephrosis

In reports such as Block s in which 19 of 41 patients recovered it is highly probable that some cases of acute glomerulonephritis are included It may be impossible to distinguish acute glomerulonephritis from lipoid nephrosis on the basis of the clinical symptoms alone Glomerulonephritis is a much more frequent cause of uremia in children than lipoid nephrosis

The Cause of Death —In 27 of our 68 cases death was due to peritonitis of which 10 were streptococcic peritonitis 7 pneumococcic and 10 unspecified In the literature peritonitis is the usual cause of death especially in the pure type According to published reports streptococcic peritonitis is about as frequent as the pneumococcic form and I cannot agree with Blackman that lipoid nephrosis is a pneumococcic infection

In 10 cases death was due to infections other than peritonitis (pneumonia 7 cases erysipelas 1, bacterial endocarditis 1 and purulent bronchitis 1) In two instances death was caused by edema of the lungs and in two it was attributed to massive bilateral hydrothorax In No 368 death was apparently due to inanition In 3 cases severe anemia was apparently the chief cause of death but it is not certain that the anemia was secondary to the renal disease In 13 cases death was due to uremia and 2 of these began as pure lipoid nephrosis and later assumed the features of the mixed form

Relation of Pure Lipoid Nephrosis to the Mixed Type —The majority of investigators believe that pure lipoid nephrosis is a distinct entity unrelated to the mixed form One may indeed set up arbitrary criteria for the pure type and reject all cases which do not correspond But this is more of the nature of an arbitrary definition than a recognition of fundamental differences since it does not dispose of the borderline cases satisfactorily No 337 corresponds clinically to the pure form except for a terminal rise ... there is a severe thickening of the capillary

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observation had not been made the case would have been entirely acceptable clinically as pure lipoid nephrosis, yet there is a severe thickening of the basement membranes

The rare cases which begin as the pure type and afterwards develop the features of the mixed form present a difficulty to those who would make a sharp distinction between the two types In

of his life he gradually developed severe hypertension and renal



Fig 49 —Serial No 363 Lipoid nephrosis From a patient who presented the clinical features of the pure type for the first five years and of the mixed type for the last two years of his illness Death from uremia Small glomeruli largely hyalinized Tubules atrophic Hematoxylin-eosin Photomicrograph

insufficiency, and died of uremia Wilbur and Brown and Woska reported cases of pure nephrosis which progressed to nephritis To escape this dilemma it has been assumed that a new disease "nephritis" is superimposed on the nephrosis, but this interpreta-

merely become more severe, no new lesion has been introduced

It may be concluded that borderline cases between the pure and mixed types of lipoid nephrosis occur and that the pure form may progress into the mixed type These transitions can only be ex

15

plained on the theory that the two forms are fundamentally related

The Nature of Lipoid Nephrosis —Before considering the various theories of the nature of lipoid nephrosis it is important to keep in mind that the characteristic phenomena of nephritis viz albuminuria and edema are due to glomerular and not to tubular injury The features characteristic of nephritis viz hypertension and renal insufficiency are due to narrowing of the glomerular capillaries regardless of the nature of the lesion which produces the narrowing

leakage of protein through the glomerular capillaries Tubular

function is seriously affected

The Nephrotic Contracted Kidney —In the patients who die of uremia the kidneys are sometimes definitely reduced in size (Nos 351 363) Microscopic study shows hyaline glomeruli and diffuse

glomerular obstruction The degree of atrophy of a tubule always proportional to the degree of capillary obstruction in its associated glomerulus When the tubules are destroyed in pyelonephritis or hydronephrosis the glomerular capillaries remain patent for months or years The tubular atrophy in lipoid nephrosis is due to disuse and anemia as it is in chronic proliferative glomerulonephritis

A number of cases have been reported in which lipoid nephrosis terminated in uremia (Debre Shapiro Wilbur and Brown Gainsborough) There were 13 deaths from uremia in our series and 10 of

view is held by
imary renal disease
ed the expression
Andrews Thomas
and Welker and others believe that there is a change in the plasma proteins which are then excreted because of their foreign character Goettsch and Reeves believe that the serum proteins in nephrosis

differ immunologically from normal serum proteins. Diebold suggests a metabolic disorder with secondary injury of the kidneys. The arguments against this interpretation have been presented in previous paragraphs. There is no satisfactory evidence that the plasma proteins are altered and this theory ignores the structural changes found in the glomeruli in all the cases of mixed type and some of the pure form.

(c) *The Nephritic Einschlag.*—This widely-accepted idea has been responsible for a great deal of confusion in the study of nephritis. The belief that hypertension and renal insufficiency in nephrosis are due to a superimposed nephritis has been generally adopted although no anatomical basis for this idea has ever been presented. As previously stated anatomical study shows that hypertension and uremia in nephroses are due to a more severe degree of the same process, i. e., thickening of basement membranes and not to endothelial proliferation. There is, however, a focal or diffuse endothelial proliferation of moderate degree in many cases but it is insufficient to produce uremia. It may be contended that this endothelial proliferation represents a terminal mild nephritis but it is also possible that it is a reaction to the same irritant that injures the basement membranes. The glomerulitis in these cases is much milder than in typical acute glomerulonephritis.

(d) *Abnormal Permeability of the Capillary Walls to Plasma Proteins.*—All the available evidence supports this interpretation. Whether the capillary walls show any visible alterations or not it is evident that they are injured since they allow protein molecules to pass through. We do not know what causes the injury but neither do we know the exact nature of the irritant which causes endothelial proliferation in glomerulonephritis. In lipoid nephrosis a relation to infection is suggested but it is not so convincing as in proliferative glomerulonephritis. Why does glomerular disease in children under ten years of age take the form of nephrosis so much more frequently than it does in adults? The glomerular capillaries of children contain a much smaller number of endothelial cells than those of adults and it is possible that this has some significance. The same injurious agent might in some patients produce no reaction, in others a thickening of the basement membranes and in others endothelial proliferation. There are numerous examples of thickened membranes with varying degrees of endothelial proliferation.

In summary it may be said that lipoid nephrosis is a glomerular disease in which the capillary walls are injured in such a way that they become permeable to the plasma proteins. The leakage of protein through the kidneys is the basic functional disturbance. Endothelial proliferation is moderate or entirely absent so that the capillary lumens remain more or less patent in most instances. Renal insufficiency and hypertension do not develop unless the basement membranes become so thick that they narrow the capil-

laries and decrease the blood flow through the glomeruli In children structural changes in the capillary walls are not often found and the disease is usually of the pure type in adults structural changes are usually present and there is commonly some degree of renal insufficiency and hypertension (mixed type) The pure and the mixed types are closely related and the former may pass into the latter From the histological point of view lipoid nephrosis is different from proliferative glomerulonephritis but it is possible that the his

disease of the kidneys as well as by proliferative glomerulonephritis

moval

of edema fluids This may sometimes be accomplished by diuretics a lo fluid intake a low salt diet or by procedures wh ch raise the

the disease to the treatment

There are several reports in the literature in which a prolonged remission of symptoms was brought about by an intercurrent attack of measles (Meizlik and Carpenter)

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Among the more frequent non-suppurative lesions are tertiary syphilis chronic arthritis and multiple myeloma Occasionally no cause of amyloidosis is found Fahr reported such a case in 1918 and there are 5 in our series in which no etiology was established The basic disturbance appears to be a continuous necrosis of tissue

Amyloid is a complex material having some resemblance to the ground substance of cartilage It is not known whether it is formed directly from necrotic tissue or whether it represents a reaction between derivatives of the necrotic tissue and blood or tissue proteins There is evidence that amyloid is carried in some form in the blood stream and that its particles are too large to pass through the pores of the glomerular capillaries

Since the disturbance of renal function is related to the amount of amyloid deposited in the kidneys our cases have been arranged in four groups Group A those with only a few glomerular capillaries filled with amyloid B those with moderate amyloid deposits but without complete obstruction of the glomeruli and without tubular atrophy C those with massive deposits in the glomeruli obstructing many of the capillaries and causing slight tubular atrophy and D those with extreme glomerular obstruction and marked tubular atrophy In tabulating our autopsy material all cases of Groups C and D are included but only those cases of Groups A and B are listed in which some important clinical data were available

Clinical Features —With the exception of cases of unknown etiology the chief clinical symptoms are usually referable to the

TABLE 32 —AMYLOID DISEASE

Group A Minimal Amyloid Deposits in the Glomeruli

Autopsy No.	Age	Sex	Disease	Albuminuria	Edema	Blood pressure	Weight of heart, gm.	Weight of kidneys, gm.	Amyloid in glomeruli	Casts	Urea nitrogen mg. per 100 cc
12 15	49	M	Tuberculosis of lungs	1	0	—	200	240	1	1	
15-261	30	F	Tuberculosis of spine	0	0		161	220	1	0	
15 292	24	M	Tuberculosis of lungs	1	1		142	353	1	1	
15-293	36	M	Tuberculosis of lungs	1	0		235	Normal	1	1	
21-494	13	M	Tuberculosis of spine	2	0		Small	Small	1	1	
22-74	65	F	Ulcerative enteritis	2	0	—	275	200	1	0	
23-29	36	M	Chronic abscess	—	0	—	240	370	1	0	
23-235	40	F	Tertiary syphilis	3	3	15_94	270	590	1	0	
25-608	38	M	Chronic osteomyelitis	3	0	—	300	625	1	2	
26-420	75	M	Tuberculosis of lungs	1	0		340	305	1	0	
26-652	23	F	Tuberculosis of lungs	1	2	110 64	200	3_5	1	0	
27-610	32	F	Tuberculosis of spine	4	1	80 50	140	300	1	0	
28 717	13	M	Transverse myelitis	3	0		Normal	Large	1	0	
29-1106	41	F	Tuberculosis of lungs	2	1	118/78	160	2 5	1	0	23
29-1642	43	M	Tuberculosis of lungs	4	0	8 40	220	360	1	0	
30-63	16	M	Tuberculosis of spine	1	1	—	150	290	1	0	
31-405	40	M	Perinephric abscess	2	2	145/90	500	235	1	0	
31 1559	39	M	Tuberculosis of lungs	0	1	170/90	215	350	1	0	
32-428	33	M	Perinephric abscess	2	3	1 6/2	115	250	1	1	
34 2016	49	F	Tuberculosis of lungs	0 4	0	110/80	225	391	1	1	70
35-1678	12	M	Tuberculosis of hip	2	0	—	240	550	1	0	10
41 278	38	M	Tuberculosis of lungs	0 3	1	130/88	345	350	1	2	14

major illness The characteristic anemia and cachexia are due more to the primary disease than to the amyloid Amyloid in the liver or spleen leads to enlargement of these organs but is not a direct cause of death Amyloidosis of the adrenals is a rare form of Addison s disease and intestinal obstruction may result from amyloidosis of the small intestines

However amyloidosis of the kidneys nearly always produces symptoms directly referable to the presence of amyloid or to changes associated with it

TABLE 33 —AMYLOID DISEASE

Group B Moderate Deposits of Amyloid in the Glomeruli No Tubular Atrophy No Renal Insufficiency

Autopsy no	Age	Sex	Disease	Albuminuria	Edema	Blood pressure	Weight of heart gm	Weight of kidneys gm	Amyloid in glomeruli	Casts	Urea nitrogen mg per 100 cc
20-367	25	M	Empyema	3	0	—	170	355	2	1	
21-52	26	F	Chron c osteomyel t s	3	3	120/82	340	680	2	2	Normal
21 523	16	F	Tubercu osis of sp ne	2	0		Sma l	Large	2	1	
24-512	28	M	Tuberculosis of lungs	3	0	—	200	560	2	1	
25 1045	23	M	Tuberculos s of sp ne	1	0	—	Normal	Norma	2	2	
26-134	15	F	Tuberculosis of h p	2	0	—	Sma	N rmal	2	0	
29-652	78	M	None	1	0	150/94	350	170	2	1	
30-214	22	F	Chron c abscess	3	3	—	190	300	2	1	
30-1203	66	M	Tertiary syphilis	2	0	140 90	400	215	2	1	
30 1295	42	F	Chron c abscess	2	0	100 96	300	465	2	0	
30-1305	29	F	Empyema	—	3	120/88		294	2	1	Normal
30-1752	48	M	Tuberculosis of lungs	3	0	80 60	218	260	2	3	29 6
31 291	47	M	Ch n c os eomyel t s	3	1	85 60	310	370	2	4	118
31 1208	21	M	Unresolved pneumon a	0	0	116/72	300	360	2	0	17 7
31 1356	35	F	Tuberculos s of lungs	4	0	95 68	340	370	2	1	
32-416	50	M	S licosis	3	0	100 60	390	4 5	2	4	95
34 1752	17	M	Chronic osteomyelitis	1	1	—	153	305	2	0	
36-1755	26	M	Tuberculos s of lungs	3	2	—	215	305	2	1	Normal
40-2148	70	M	Suppurat ve my l s	0 3	0	—	2 5	4 5	2	1	54
43 332	37	F	Ovarian abscess	2	0	—	275	430	2	0	
43 1636	75	F	Carc of rectum		0	4 138	530	340	2	1	
43 2418	58	M	Pulm. tubercul s s	3	1		500	113		0	NPN 166
46 160	76	M	None	3	4	140/90	300	408	2	0	16
47 1167	59	M	Pulm tuberculos s	0 4	2	106 86	250	510	2	0	— PP 39

Albuminuria —Albuminuria is present in over 90 per cent of cases of renal amyloidosis and is usually more severe in the late than in the early stages It is the first evidence of renal involvement The duration of albuminuria prior to death varies from a few months to ... uminuria ... nal amy ... used by ... 32 and 35 shows however that albuminuria is so ... ith slight renal amyloidosis (Group A) and occasionally there is only a slight albuminuria with severe amyloid deposits

TABLE 34 — AMYLOID DISEASE

Group C Marked Accumulation of Amyloid in the Glomeruli A Little Tubular Atrophy Often Some Renal Insufficiency

Autopsy no	Age	Sex	Disease	Albumin na	Edema	Blood pressure	Weight of heart gm	Weight of kidneys gm	Amyloid in glomeruli	Casts	Urea nitrogen, mg per cent
13 16	31	F	Tuberculosis of lungs	—	0	—	—	Small	3	0	
15 41	34	M	Tuberculos s of lungs		0	—	293	437	3	3	
20-451	12	M	Tuberculos s of lungs	3	0	—	145	325	3	1	
24-572	14	F	Chronic abscess	3	0	—	Normal	Large	3	3	
27 806	25	F	Empyema	3	"	—	223	445	3	2	
28-145	48	M	Tuberculosis of lungs	—	0	—	233	505	3	1	
28-372	51	M	Pyonephrosis	3	1	110 60	230	700	3	1	
28-545	18	M	Transverse myel t s	4	1	—	Normal	Large	3	2	
29-1804	50	F	None	1	2	170/120	435	215	3	0	52
30-533	23	M	Tuberculos s of spine	2	1	110/70	300	800	3	4	
30 982	46	M	Pyonephros s	4	1	98/48	—	590	3	3	121
30-1389	33	M	Tuberculos s of lungs	4	1	105 72	315	435	3	1	178
30 1572	49	M	Tuberculosis of lungs	3	0	136/104	505	652	3	1	65
31 1482	58	M	Tuberculosis of lungs	4	3	—	272	416	3	0	10 7 9 da
31 1754	46	M	Empyema	3	1	238/142	375	3 5	3	3	
31 1877	43	M	Tuberculos s of lungs	2	0	90/58	300	380	3	4	
31 1934	47	F	Chron c arthritis	3	4	170/70	200	220	3	2	9 4
31 2015	8	M	Tuberculosis of spine	1	4	—	72	135	3	0	
32 362	43	M	Tuberculos s of lungs	4	3	110/90	265	400	3	0	
32 1850	36	M	Tuberculos s of lungs	4	0	—	275	375	3	0	11
33 1325	15	F	Chron c osteomye tis	{0 3	1	—	150	470	3	0	
33 1649	53	M	Chronic osteomyelit s	3	1 0	110/68	450	250	3	0	NPN 68
34-712	53	M	Chronic arthrit s	4	0	150/84	440	470	3	1	121
34-1923	37	M	Tuber ulosis of lungs	{0 3	0	110/70	2 5	299	3	2	50
35 1834	30	F	Tuberculosis of lungs	3	3	—	300	455	3	0	NPN 26 a 3 0* g 3 6*
36-70	37	F	Tuberculos s of lungs	1	0	—	361	673	3	3	
36-820	50	M	Tuberculosis of lungs	2	1	—	235	380	3	4	NPN 102
37 188	22	M	Chronic osteomyel tis	{1 4	3	—	410	394	3	0	51
38-106	69	M	Perinephric abscess	3	0	148 68	325	320	3	3	116
39-1216	26	M	Chronic osteomyel tis	1	0	120 70	340	640	3	3	66 6 a 2 5* g 3 1
39 1483	51	F	Tuberculosis of lungs	3	3	150/100	213	670	3	4	NPN 84 a 1 70 g 2 14 f 0 16
39 2781	33	M	Tuberculosis of lungs	{0 3	0	—	270	400	3	3	a 2 15 g 1 47
40-954	73	M	Tuberculosis of lungs	3	0	—	364	310	3	4	NPN 40
40 2385	56	M	Pulm tuberculosis	{0 3	0	160 90	390	L 155	3	0	NPN 69
41-680	65	M	Pulm tuberculosis	3	2	124 86	255	378	3	1	50 PP 3 3 gm
41 1906	29	F	Pulm tuberculosis	3	3	—	107	290	3	1	—
41 2731	50	M	Chronic rheumatoid arthritis	3	1	130/95	330	365	3	0	PSP, 8%
41 2673	54	F	Chronic rheumatoid arthritis	?	2	120 80	350	Large	3	1	23 a 2 8 g 3 4
42-1082	59	M	Nephrolithiasis	4	0	150/70	350	R 75	3	4	23
42 1340	60	M	None	3	1	145/90	340	385	3	—	25 PP 4 57
42 2130	30	M	Pulm tuberculosis	4	0		250	570	3	4	NPN 91

TABLE 34 —AMYLOID DISEASE—*Continued*

Group C Marked Accumulation of Amyloid in the Glomeruli A Little Tubular Atrophy Often Some Renal Insufficiency

Autopsy No	Age	Sex	Disease	Albuminuria	Edema	Blood pressure	Weight of heart gm	Weight of kidneys gm	Amyloid in glomeruli	Casts	Urea nitrogen mg per cent
44-307	49	M	Rheumatoid arthritis	3	3	118/68	?98	27?	3	0	29 P P 3 5 gm
44 1315	?6	M	Osteomyelitis	—	0	—	2?0	565	3	2	H gb
44 1533	37	F	Pulm tuberculosis	2	0	—	193	314	3	4	
44 1905	38	M	Pulm. tuberculosis	0	0	130 85	314	300	3	4	
45-61	40	M	Pulm tuberculosis	3	0	11?/68	370	594	3	4	73
45-310	68	M	None	3	1	130/80	360	295	3	3	57 P.P 5 7
45 1970	61	M	Rheumatoid arthritis	{0 {3	1	1?0/?8	450 (valve)	310	3	4	
46 1565	59	M	Pulm tuberculosis	—	0	14?/80	300	6?0	3	4	
46-?454	24	M	Pulm tuberculosis	{0 {2	4	—	?00	400	3	0	P P 3 5 gm
48 54	63	F	Rheumatoid arthritis	{1 {3	2	118/70	?50	115	3	4	109
48 9?3	57	M	None	2	4	130/7?	340	?50	3	4	76 Cholest. 119
48 1123	46	M	Rheumatoid arthritis	1	?	1?0/70	7?0 (valve)	2?0	3	1	66

a Plasma albumin g plasma globulin f fibrinogen P P total plasma proteins, gm. per cent.

TABLE 35 —AMYLOID DISEASE

Group D Extreme Filling of the Glomerular Capillaries With Amyloid Marked Tubular Atrophy Uremia

Autopsy no	Age	Sex	Disease	Albuminuria	Edema	Blood pressure	Weight of heart gm	Weight of kidneys gm	Amyloid in glomeruli	Casts	Urea nitrogen, mg per 100 cc
16-45	61	M	Tuberculosis of lungs	2	2	—	550	Small	4	2	
20-84	59	F	Tertiary syphilis	—	1	—	300	520	4	4	
21-457	59	M	Tuberculosis of lungs	3	0	—	2?5	370	4	1	
25-204	19	M	Tuberculosis of h p	1	3	—	Normal	Large	4	1	
28-64	35	F	None	3	0	190/110	355	260	4	1	147
28 217	58	M	Bronchiectasis	2	0	—	435	240	4	4	
28 1214	15	M	Chronic osteomyelitis	3	0	—	Normal	Large	4	2	
29-1616	55	M	None	4	1	104/50	490	280	4	0	134
29-16?9	27	M	Chronic osteomyelitis	4	1	110/ ?	2?0	5?5	4	4	68
29-1425	54	M	Ulceration of legs	4	0	1?0/60	5?0	440	4	4	134
32-52	43	M	Tuberculosis of lungs	0	0	—	375	3?0	4	1	
32 175	75	M	Tertiary syphilis	4	4	110/64	—	240	4	1	NPN 58 8
32 1369	19	F	Tuberculosis of h p (albuminuria 8 yrs)	{2 {4	0	—	230	275	4	4	203
32-1726	47	F	Tuberculosis of lungs	{2 {4	0 3	135/70 170/110	350	385	4	0	77 7
33-67	29	F	Tuberculosis of lungs	4	0	100/70	210	475	4	4	193
33 1793	28	M	Chronic arthritis	3	1	64/40	250	210	4	3	123 a 4 29* g 2 43 f 0 18
34-904	40	M	Tuberculosis of lungs	2	3	—	315	500	4	0	217
34-925	23	M	Chronic osteomyelitis	3	0	{185/114 {170/120	352	245	4	0	
34-1117	33	M	Pelvic abscess	3	0	128/68	420	450	4	0	NPN 212
35-735	32	M	Tuberculosis of lungs	4	3	{130/88 {149/102	404	180	4	0	NPN 11

TABLE 35 —AMYLOID DISEASE —*Continued*

Group D Extreme Filling of the Glomerular Capillaries With Amyloid Marked Tubular Atrophy Uremia

Autopsy No	Age	Sex	Disease	Albuminuria	Edema	Blood pressure	Wt. of heart, gm.	Weight of kidneys gm.	Amyloid in glomeruli	Casts	Urea nitrogen mg per 100 cc.
35-1548	53	M	Tuberculosis of lungs	4	0	125/80	2 5	3.0	4	0	NPN 96 8
35-2092	18	M	Chronic osteomyelitis	"	0	170/110	—	367	4	0	73
36-1490	35	M	Chronic arthritis	0 3	0	145/90 166 96	400	10o	4	0	NPN 250
36-1874	47	M	Tuberculosis of lungs	1 4	0	110/60	393	260	4	0	30 (7 mo)
37-690	40	F	Tuberculosis of spine	+	1	—	300	255	4	1	NPN 115
37 709	68	M	Tuberculosis of lungs	4	3	170/78	240	190	4	2	100
38 33	55	M	None	3	0	110/62	375	300	4		
38-185	36	M	Chronic osteomyelitis (26 yrs)	3	0	204/110	430	150	4	0	NPN 302
41 760	54	M	Rheumatoid arthritis (20 yrs)	2	2	110 50		240	4	0	
41 1876	35	F	Osteomyelitis (21 yrs)	3	0	150/88	290	160	4	0	124 P P 4 7
4 784	30	M	Osteomyelitis (20 yrs.)	4	3	196/130	605	260	4	4	UN 175
41-474	51	M	Pulm tuberculosis	4	0		475	(R 210	4	3	60
41 1457	60	M	Pulm. tuberculosis	3	0		450	332	4	3	
41 2 14	34	M	Rheumatoid arthritis	0 4	2	150/90	320	330	4	3	High
42-833	39	M	Pulm. tuberculosis	0 4	2	130/95	336	3 4	4	3	NPN 87
42 1 8	43	F	Pulm tuberculosis	0 2	1	—	170	250	4	1	P P 3 58
43 659	6	F	Rheumatoid arthritis	1 4	1		350	378	4	2	
43 146	66	F	Abscess of kidney	+	0	160 82	410	270	4	3	67
46-253	4	F	Bronchiectasis	1	0	130 76	3 5	270	4	4	
47 0 8	58	F	Pulm tuberculosis	—	0		250	31	4	1	
47 2499	5	M	Bronchiectasis	3	0	126/84	240	130	4	3	82 P P 6 8 gm
47 2 02	5	M	Pulm. tuberculosis	1	2	116 68	300	294	4	2	5 P P 4 5 gm
47 272	44	M	Rheumatoid arthritis	4	0	19 ? 140 60	5. 0	5	4	3	200
47 2 36	9	M	Rheumatoid arthritis	4	4 0	104 64	290	240	4	1	101
47 274	56	M	Pulm tuberculosis	1	3	112 84	500	375	4		P P 4 5 gm.
48-4 52	1	M	Tuberculosis of hip	4	1		18	200	4	1	60

a Albumin g globulin f fibrinogen P P plasma proteins

The protein in the urine escapes from the blood through injured glomerular capillaries Evidently some protein escapes from capillaries which do not contain amyloid It is not clear in what way the amyloid deposit promotes the leakage of protein but it may do so by obstructing their lumens and increasing intracapillary blood pressure or by destruction of the basement membranes

The Urinary Proteins —There are comparatively few studies available on the composition of the urinary proteins in amyloid disease but the observations indicate that the proportion of globulin is greater in amyloid disease than in other albuminurias Geill found the albumin fraction from 35 to 60 per cent in amyloid disease

whereas in glomerulonephritis and lipoid nephrosis it is usually about 90 per cent

Hiller McIntosh and Van Slyke found the albumin globulin ratio of the urinary proteins usually above 10 in nephrosis between 5 and 10 in acute nephritis and usually below 5 in chronic nephritis with retention of urea In 1 case of amyloid disease the albumin globulin ratio was 1 5

Lemierre and his associates studied the urinary proteins in a case

Three examinations

n 1 35 albumin 0 63

m per liter of urine

The Plasma Proteins —A few observations are available on the *plasma proteins in renal amyloidosis* Linder *Maxwell and Green* found the plasma proteins 3 8 to 4 7 gm in a boy with marked *retention of urea Apparently some of the observations were made* when the patient was free of edema Bannick and Barker in a patient with *moderate renal insufficiency but without edema found* the total protein 3 8 gm of which 27 per cent was albumin Lemierre and his colleagues made three determinations of the plasma proteins on a patient with renal insufficiency but without edema albumin 3 26 globulin 3 22 albumin 3 27 globulin 3 19 albumin 2 45 globulin 2 29 gm per cent Shapiro s patient had severe albuminuria and edema with serum albumin 0 38 and globulin 1 74 gm Achard reported a case with severe albuminuria and edema of the ankles who had a total protein of 6 3 gm (albumin 1 9 globulin 4 4)

We have observations on 17 cases (Tables 34 and 35) The proteins were reduced in 15 of the 17 cases and the reduction of albumin is usually sufficient to explain the edema

These observations *are sufficient to show that the plasma proteins* may be reduced moderately or severely in renal amyloidosis The *reduction usually affects the albumin more than the globulin fraction* and is presumably due partly to the loss of protein in the urine and partly to malnutrition

Blood Cholesterol —I have been able to find only a few observations on blood cholesterol Linder and associates found cholesterol 330 to 920 mg per cent in a patient with edema and low plasma proteins Lemierre found cholesterol 230 to 358 mg in a patient with decreased plasma proteins but without edema Shapiro s patient had 400 mg cholesterol and Achard s had 201 mg per cent

The values

admittedly in

creases with

the decrease of plasma proteins as it does in lipo[id neph]rosis

Edema —*Edema* is a variable feature in amyloid renal disease Altnow found that one-fourth of the patients have edema at some time during the early and middle stages of the disease and that

about two-thirds have terminal edema Edema was present at some time in 69 of our 145 cases It is occasionally more severe in the late than in the early stages, but there is no evidence in our records

without edema

Fahr has also noted that there is no connection between the severity of the glomerular lesions and edema In a group with 4 and absent 2 and absent is present in 3 and absent in 2

In 30 of our cases of chronic suppurative diseases, the majority of which had amyloid in the liver and spleen but none of which had amyloid in the kidneys, edema was absent in 12, slight in 12, moderate in 3 and severe in 3 Edema is obviously not due to the presence of the amyloid deposit It is probably caused by depletion of the plasma proteins brought about by albuminuria and malnutrition

Hematuria —A mild hematuria is occasionally found in amyloid disease (Bannick and Barker) but it is seldom as conspicuous as in acute glomerulonephritis The erythrocytes escape from injured capillaries that are not filled with amyloid

The Blood Pressure —A majority of investigators find no hypertension with amyloid disease of the kidneys Cases without renal insufficiency or hypertension have been reported by Fahr (6 cases), McElroy (1 case), and Shapiro (1 case) Cases with renal insuf-

Below 120 mm Hg, 20 cases 120 to 150, 11 cases, 150 to 180, 4 cases Altnow found hypertension in only 3 of 57 patients, and in 2 of these the hypertension developed during the course of the amyloidosis

tension Berblinger reported the case of a woman aged forty-one years who had suffered from an infection for thirty years There

was severe albuminuria During the last year of life the blood pressure rose to 215/140 and retinitis developed The non protein nitrogen ranged from 73 to 91 mg per cent

The blood pressure was recorded in 84 of our 145 cases Twenty one of the 84 patients had a systolic pressure of 150 mm Hg or

showed arteriolosclerosis

In Group C 6 of 31 patient and in Group D with severe amy

that severe amyloidosis may cause hypertension since in Group D with severe amyloidosis and renal insufficiency 8 of 14 patients under forty years of age had hypertension The absence of hyper tension in the majority of cases is unexplained but may be due in part to the cachexia so often associated with advanced amyloid disease

Renal Insufficiency in Amyloid Disease —It is well established that amyloid disease may terminate in uremia Cases terminating

blood urea and in one of these the tubules are extensively ob[illegible] by casts

Twenty three of the 31 cases in Group C on which functional studies were made showed more or less nitrogen retention With one exception the 31 cases of Group D had nitrogen retention at uremic levels In No 36 1874 the last determination was made seven months before death All of the cases in Group D showed con vincing histological evidence of severe renal insufficiency which was due largely to obstruction of the glomerular capillaries but partly in some instances to obstruction of the tubules by casts *It may therefore be said that amyloid renal disease frequently terminates in uremia*

Summary of the Clinical Picture —In the vast majority of cases of amyloid renal disease the diagnosis is easily made because of the associated chronic infectious process Most often the underlying disease is tuberculosis but often it is a non tuberculous process such as chronic osteomyelitis empyema bronchiectasis *tertiary* syphilis or chronic rheumatoid arthritis The initial symptom of renal involvement *is albuminuria* which usually becomes rather

In Sh piro s patient
in 7 of our
considered
12 (Table 33)
a clinical diagnosis of lipoid nephrosis w is m de and in this case amyloid was found nly in the ki lneys In the cour e of months or years symptoms and signs of renal insufficiency develop and the bloo l pressure may become elevated In such cases there is a

rosis or chronic glomerulonephritis

The Congo Red Test —Ten to 15 cc of a 1 5 per cent aqueous solution of Congo red is injected intravenously The amount in the blood at the end of four minutes is compared with the amount at the end of one hour The test is consi lered positive if over 40 per cent of the dye disappears from the blood during the first hour The dye is absorbed by the amyloid When amyloid is limited to the kidneys only a little of the dye is absorbed and hence the test is negative

Size of the Kidneys —In amyloid disease the kidneys are usually larger than normal (Fig 50) but they may be contracted In 41

after which there is a gradual decrease in size as a result of tubular atrophy Uremia may develop wh le the kidneys are still large Markedly contracted kidneys such as are common in chronic glo merulonephritis are unusual in amyloid disease—in only 10 cases was the c mbined weight less than 200 gm but 1 instance of ex treme contraction was foun l (No 36–14J0 Table 35)

Alterations in the Glomeruli The glomeruli are nearly always involved even in the earliest stages of renal amyloidosis an l the disturbances of renal function are caused chiefly by leakage of

lumens (Figs 51 52) At no time is amyloid found external to a demonstrable basement membrane In the early stages it is usually possible to demonstrate the membrane distinctly from the amyloid but sometimes the amyloid blends with the membrane from the first When the capillary is well filled the distinction between membrane and amyloid is usually lost but sometimes the membrane is clearly demonstrable

An increase of endothelial nuclei is frequently observed in capillaries without amyloid as well as in those that contain amyloid but this endothelial proliferation never reaches the degree char



FIG 50 —Amyloid disease of the kidney Photograph

is superimposed on acute glomerulonephritis or any other form of renal disease

As the amyloid accumulates the capillary may undergo a progressive enlargement attaining two or three times its normal ... permeable

Ultimately the glomerular capillaries are completely blocked by amyloid, the glomerular circulation ceases, and disuse atrophy of the associated tubule sets in The ultimate result of diffuse tubular [illegible]

from those of chronic glomerulonephritis and primary hypertension in that the hyalin is derived from amyloid and not from capillary basement membranes

Casts —Casts play an important rôle in the amyloid kidney They do not give the amyloid reaction, but they are apparently of firmer structure than ordinary casts since they have a great tendency



FIG 51 —Amyloid disease of a glomerulus The amyloid is first deposited within the capillary lumens Later the entire capillary is filled Photomicrograph

to lodge in the tubules Obstruction of the lumen causes dilatation and sometimes atrophy of the tubule They are sometimes more important than the glomerular lesions in causing renal insufficiency (Table 33, Nos 31–291 and 32–416)

[illegible]

acteristic of primary hypertension An early amyloid deposit is easily distinguished from hypertension, but a massive amyloid accumulation obscures the evidences of hypertension The involve-

ment of the arterioles is often a prominent feature and arteriolar narrowing is often a factor in the destruction of the kidney

The Medulla —One of the most frequent sites of the amyloid deposit is the medulla The amyloid accumulate chiefly in the walls of the vasa recta and in the interstitial tissues to a lesser



FIG 59 —Early stage of amyloid deposit in a glomerulus The amyloid is laid down internal to the basement membranes Mallory Heidenhain stain Photomicrograph

extent under the basement membranes of the medullary tubules Rarely there is sufficient amyloid in small areas to destroy tubules and produce focal cortical atrophy

The Tubules —In occasional instances cortical tubules are ... ment mem ... nate leaving ... often seen in some of the proximal convoluted tubules ... alteration is seen much more frequently in moderately advanced stages than in uremic amyloid kidneys Fahr believes that hyaline granular

the function of the tubular epithelium

In conclusion it may be said that amyloidosis is a special type of renal disease In some instances it exhibits the clinical features of lipoid nephrosis and in others it resembles chronic glomerulo-



FIG 53 Amyloid contracted kidney with uremia Note hyaline glomeruli and severe tubular atrophy Photomicrograph

nephritis, and occasionally the disease progresses from a picture of nephrosis to one of nephritis, but it does not clarify our conceptions to force the disease into either of these groups

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D THE TOXEMIAS OF PREGNANCY

On a pathological basis the toxemias of pregnancy may be classified as follows

1 [illegible] (early pregnancy)
2 [illegible]
3 Preexistent primary hypertension
4 Eclampsia (late pregnancy)
   (*a*) Preeclampsia (non-convulsive toxemia)
   (*b*) Eclampsia (convulsive toxemia)

[illegible]

occurs [illegible] *increase in the severity of all symptoms referable to the renal disease* The anatomical form of the renal disease is apparently not important, but most of the cases are chronic glomerulonephritis and a few are bilateral polycystic *renal disease* *When the renal insufficiency is slight pregnancy may be normal throughout, but when it is moderate or severe complications always develop* See pages, 98 201

When the renal insufficiency is severe pregnancy usually terminates in abortion during the first few months, but when it is only moderate the symptoms may first become pronounced during the latter part of pregnancy, and these cases are difficult to distinguish from preeclampsia and eclampsia *unless the patient has*

been studied prior to the pregnancy or during the first trimester

A nephritic toxemia of late pregnancy may therefore be confused [illegible] postmortem the liver shows no [illegible]

[illegible]

that the best functional renal test is pregnancy After the termination of pregnancy the renal symptoms usually improve but do not [illegible]

To[illegible] D[illegible] Pre[illegible] H[illegible]

[illegible]

hypertension from preeclampsia and many obstetricians do not attempt to do so We, therefore, have no reliable statistics as to the frequency of this complication However, there is some evidence that a fair proportion of preeclamptic toxemias are on the basis of primary hypertension Weiss found that about one-third of his cases of toxemia had hypertension before pregnancy It has been emphasized by several writers that toxemia in a subsequent pregnancy occurs nearly twice as often after non-convulsive toxemia (preeclampsia) as after eclampsia (Dieckmann) This observation lends strong support to the view that many cases of preeclampsia represent pregnancy in a woman with primary hypertension Browne states that 25 per cent of all cases of toxemia are due to preexistent hypertension

It is well known that a woman with primary hypertension often experiences an increased severity of her symptoms during pregnancy The blood pressure attains a higher level and albuminuria and edema may develop Symptoms often appear during pregnancy in a woman who previously had no complaints If the systolic blood pressure was found below 130 mm Hg before the onset of pregnancy or during the first trimester, it may be safely assumed that a hypertension in the third trimester represents preeclampsia, but pressures between 130 and 140 mm Hg during these earlier periods may represent primary hypertension, and pressures above 140 mm Hg mean definite hypertension

An example of pregnancy in a woman with primary hypertension follows

Gravida II, aged thirty eight years, was admitted January 18 1928 Expected date of confinement, March 22 Said to have had a few convulsions during her first pregnancy, fourteen years previously Under treatment for hypertension the past five years Systolic blood pressure [illegible] ortly after the onset of [illegible] 5/120 and during the [illegible] 170/110 She entered the hospital because of visual disturbances, edema and vomiting For two

months before admission she had been troubled with headaches and dizzi

There were no convulsions

The postmortem revealed passive congestion of the liver but no necroses The kidneys showed a generalized arteriolosclerosis without atrophy of the parenchyma

It may be concluded that many cases of preeclampsia are due to primary hypertension It is not safe to assume that hypertension persisting after labor is caused by the preceding toxemia of pregnancy

4 **Preeclampsia and Eclampsia** —Preeclampsia is used by most writers to designate *non-convulsive toxemias of late pregnancy*

tion can be drawn between convulsive and non convulsive eclampsia In general convulsive eclampsia is a more severe stage of the disease but many patients die without having had convulsions and at autopsy the characteristic changes are found in the kidneys and liver Convulsions are not a necessary feature of eclampsia

Clinical Features —The characteristic symptoms and signs are convulsions hypertension albuminuria edema headache visual disturbances nausea and vomiting vertigo restlessness and especially in fatal cases coma These symptoms are by no means all present in every instance and apparently no single symptom is invariably present

Frequency —Hauch estimated the frequency of eclampsia in ... 17 per cent) Seitz ... The rate in Baden ... Greenhill reported ... Weintraub 63 in ... 7 per cent) Torpin and Coppedge found the incidence in 10 000 white women about 1 per cent and in 11 300 negro women about 1 6 per cent Hoffstrom gave the incidence of eclampsia and preeclampsia as 1 ?5 per cent in 19 215 births Schmechel at Dresden found 0 9 per cent in ... 0 8 ... in 13 139 births ... nt in ... to 1 ... the different reports A part of ... cy is no ... o the fact that some writers are re... eclam... lampsia and others only convulsi... Anoth... igh incidence in cert... spitals ... wh... h ... who

Eclampsia is much more frequent in primiparæ than in multiparæ. The usual hospital statistics show 70 to 80 per cent of eclampsia in primiparæ. Strober in 336 instances of eclampsia found 71.1 per cent in primiparæ and 28.8 per cent in multiparæ. Mudaliar in 148 cases found 66.9 per cent in primiparæ. Hoffstrom in 19,215 births reported eclampsia in 0.42 per cent of the multiparæ and 2 per cent of the primiparæ. Buttner in 179 cases of eclampsia found 60.2 per cent in primiparæ and 39.8 per cent in multiparæ. On the basis of the relative frequency of primiparous and multiparous births Buttner calculated that eclampsia occurs in 0.37 to 0.45 per cent of the former and 0.077 to 0.091 per cent of the latter. The statistical data therefore indicate that the liability to eclampsia is four to five times as great in primiparæ as in multiparæ. No satisfactory explanation for this difference has been offered. A possible explanation may be that those women who have eclampsia at the first pregnancy try to avoid subsequent pregnancies and are therefore excluded from the multiparous group.

There is apparently an increased tendency to eclampsia with multiple births. Hoffstrom reported on 19,215 births of which 18,449 were single births, 364 twins and 3 triplets. The incidence of eclampsia was 1.44 per cent in the single and 8.13 per cent in the multiple. In 1036 cases of eclampsia Tillman and Watson found 31 twin pregnancies.

Page believes that there is a greater incidence of toxemia with hydatiform moles than with intrauterine pregnancy. Among 30 moles he found 10 cases of preeclampsia. Wigger reported a case of eclampsia resulting from an hydatiform mole and gave references to 8 other similar cases.

Eclampsia may develop as a complication of tubal (Ebeler) or ovarian pregnancy (Lunkewski).

Period of Gestation.—Eclampsia rarely develops before the fifth month of gestation and only a few cases occur before the sixth month. Fehling in a survey of 516 cases found only 5 before the fifth month. A good survey of the literature of early eclampsia is given by Ebeler who found reports of 55 cases before the fifth month. Luth doubts some of the early cases; in a survey of 56 published reports he stated that there were only 11 postmortems and that the details of these were rather meager. In toxemias developing before the fifth month there is a strong probability of underlying renal disease or primary hypertension. Goedecke gives the following distribution of 306 cases of eclampsia based on the weight of the fetus: second to third month 1, fifth to sixth month 13, *sixth or seventh month 39, seventh to eighth month 53*, eighth to ninth month 85, ninth to tenth month 38, full term 77 cases. In our 59 fatal cases death occurred in the stage of pregnancy indicated as follows: fifth to sixth month 1, sixth to seventh month

5, seventh to eighth month 5 eighth to ninth month 10 ninth t
tenth month 15 at full term 23 cases

In an analysis of 384 cases Goedecke found that the first convul sion occurred postpartum in 70 (18 2 per cent) Peckham in report of 77

and 15 post[illegible]

partum 10 [illegible]

postpartum 11 8 per cent Meyer Wirz reported 62 antepartum 3 intrapartum and 23 postpartum Strober in 330 cases found that 23 7 per cent began antepartum 56 2 per cent intrapartum and 20 per cent postpartum It is not clear in any of these statistics how often preeclamptic symptoms were present before labor in the group in which the first convulsion occurred postpartum

It is to be noted that eclampsia develops in the vast majority of instances after the fetus and placenta have attained considerable size The death of the fetus *in utero* does not relieve the symptoms but in a majority of cases emptying of the uterus produces relief The postpartum convulsions might be explained on the assumption that the hypothetical toxic substance is not yet completely eliminated from the blood Eclampsia rarely sets in later than twenty four hours after labor

Onset Seitz states that in about 80 per cent of cases of eclampsia preeclamptic symptoms are present before the onset of convulsions Wolff and Zade also find a gradual onset of symptoms in the usual case Three of our patients were found dead and in 3 others the duration was unknown Two patients were studied carefully and exhibited no signs of toxemia until after the completion of labor In the remaining 51 cases there were preeclamptic symptoms varying in duration from five hours to six months In 23 patients the duration of toxic symptoms was one week or less and in 7 of these the duration was twenty four hours or less Thirteen patients had

ly of 10 000 cases of ded that convulsive equent pregnancies

Schmechel traced 83 women who had pregnancies subsequent to eclampsia Of these 15 (18 per cent) had a second attack of eclampsia Young traced 42 women who became pregnant again after an attack of eclampsia In the 60 gestations which occurred there were 3 instances of eclampsia

Page and Cox in a study of 57 pregnancies subsequent to eclampsia found that 12 women (21 per cent) had a second attack These writers collected from the literature 747 cases of eclampsia studied in later pregnancies Eclampsia recurred in 10 5 per cent In our 59 cases 1 woman died in the second and 1 in the third attack of convulsive eclampsia

The above data indicate that convulsive eclampsia recurs in less

than 10 per cent of subsequent pregnancies But a high percentage of the pregnancies after eclampsia are accompanied by some abnormality Schmechel traced 83 women in subsequent pregnancies and found that 42 per cent had normal pregnancies 40 per cent had preeclampsia and 18 per cent had eclampsia Young found that of 60 gestations in 42 women after eclampsia 15 were accompanied by albuminuria 6 by abortion hemorrhage or premature labor and 3 by eclampsia—40 per cent of the subsequent pregnancies were abnormal

Preeclampsia is said to show a higher incidence of toxemia in subsequent pregnancies than eclampsia Dieckmann reported that of 225 women with non convulsive toxemia 27 per cent had normal subsequent pregnancies and 73 per cent had a repetition of the

are attended with some form of toxemia and that about 50 per cent of pregnancies after non convulsive toxemia are so complicated Chesley and Somers in a follow-up study of 155 women who had had eclampsia found that toxemia recurred in 47 per cent of subsequent pregnancies

It is widely believed that permanent hypertension is induced by the hypertensive toxemias of pregnancy but this is not a necessary conclusion from the available evidence The high frequency of recurrence of non-convulsive toxemia may mean merely that such women have a primary hypertension which is aggravated by pregnancy (Dieckmann) Hypertension is found in about 50 per cent of women past middle life Certainly one should not attribute to pregnancy everything that happens thereafter

An interesting report was made by Breaky who traced 115 survivors of eclampsia and 218 women after normal pregnancies Hypertension (150 mm Hg or higher) was found in 26 5 per cent of the eclamptics and 21 6 per cent of the normal controls Albuminuria was found in 6 38 per cent of the eclamptics and 2 per cent of the controls

Convulsions Convulsions are the characteristic feature of eclampsia but not a necessary part of the picture since many fatal cases without convulsions show the characteristic lesions in the liver and kidneys In 19 of our 59 fatal cases no convulsions occurred The number of convulsive attacks is variable Some patients have tremors but not true convulsions The convulsive seizures commonly follow but may occasionally precede the preeclamptic symptoms The convulsions are commonly attributed to injuries of the central nervous system caused by arteriolar spasm and this view is supported by the frequent finding of small areas of softening and hemorrhage in the brain

Edema —The edema associated with pregnancy is not well under-

stood but there are several influences which may play important roles The edema of the ankles which is found at times in nearly all pregnant women during the last two months of pregnancy is probably due in part at least to increased venous pressure in the lower extremities resulting from the pressure of the uterus on the iliac veins The venous pressure in the legs reaches a level of 31 4 cm water in the last two months (Strauss) Many investigators also find a moderate increase of venous pressure in the arms in late pregnancy

A generalized edema of varying degree is found in about two-thirds of all normal pregnant women An unusual increase of weight during pregnancy is often due to retention of water although no clinical edema may be noted Dieckmann believes that a gain of over 600 grams per week is abnormal and indicates retention of water

and Wegner found a range in different individuals from 6 to 8 9 gm per cent and at the end of pregnancy the plasma proteins were on the average 7 per cent below the level of the first trimester

plasma volume and the total plasma proteins but that the proteins

the plasma is some-
the slight increase
of venous pressure might be sufficient to produce edema However the majority of investigators believe that these influences are insufficient to explain the edema of pregnancy and prefer to attribute it to some unknown disturbance in the electrolytes which leads to retention of water in the tissues

The percentage of fibrin in the blood shows an average increase of about 10 per cent at term but this protein exerts very little osmotic pressure

In eclampsia the intensity of edema varies greatly Mudaliar and associates in 148 cases found edema absent in 10 8 mild in 17 6 moderate in 43 2 and severe in 28 4 per cent They believe that the prognosis is worse in those without edema In our 59 fatal cases edema was absent in 24 slight in 21 moderate in 7 and severe in 7 Edema is therefore not a necessary part of the eclamptic
ts severity and
of the
ed with

more serious toxic symptoms

The Urine —Albumin is found in the urine in practically all cases of eclampsia Usually it is present in large amounts but occasionally there is only a trace It may appear in the urine or increase greatly in amount within a short time so that repeated examinations are necessary to exclude its presence Usually albuminuria precedes the other symptoms but rarely it is first found after the convulsions One hesitates to make a diagnosis of eclampsia in the absence of albuminuria but such cases have been published (Goedecke, Hiess and Beckmann, Austin, Meyer-Wirz, and Breuning) Albuminuria

npsia There was ntity of urine was resumably due to retention of water by the tissues and not to renal damage, except in the rare cases of cortical necrosis

In our experience there was no notable reduction of the *specific gravity* of individual samples of urine Chesley states, however, that more than half of eclamptics cannot concentrate above 1 023—a phenomenon which he correctly attributes not to renal disease *but to the oliguria which results in decreased excretion of urea,* since more urea is reabsorbed from the glomerular filtrate in a low diuresis A low-salt diet also tends to lower the specific gravity of the urine

Erythrocytes are often found in the urine in increased numbers but they are seldom as numerous as in acute glomerulonephritis Gross hematuria is not seen except in association with cortical necrosis

Renal Function —Heynemann found the non-protein nitrogen of the blood nearly always normal or only slightly elevated Hussy never found it above 50 mg per cent Seitz found the non-protein nitrogen above 40 mg in about one-half of his cases and above 60 mg in 10 per cent In 5000 normal pregnancies Caldwell and Lyle found the average non protein nitrogen 35 mg, urea nitrogen 18 mg, and uric acid 3 mg There was no increase during the

changes in the kidneys were not different from those without retention of metabolites but in one case No 42–1602 there was a complicating pyelonephritis Presumably oliguria and extrarenal influences contribute to produce nitrogen retention in some cases

The phenolsulphonephthalein test has little value because of the oliguria which causes retention of a large fraction of the dye in the pelves and ureters

Cambier and Snoeck found the excretion of creatinine normal in

eclampsia except during an eclamptic crisis when it is notably reduced

We may conclude that there is often a slight and rarely a severe nitrogen retention in eclampsia but that apart from the cases of cortical necrosis there is no serious damage to the kidneys

Chesley and associates (1940) and Welsh Wellen and Taylor (1942) measured the renal blood flow by the diodrast clearance in women with normal pregnancy and in women with eclampsia and preeclampsia They found a normal renal blood flow in both normal and eclamptic pregnancy In essential hypertension the filtration fraction is increased presumably because of constriction of the efferent glomerular arterioles but in eclampsia the filtration fraction is normal or diminished Chesley and associates suggest that in eclampsia the capillary lesion interferes with the filtration of water Since the renal blood flow is normal in eclampsia hypertension can not be attributed to renal ischemia

In a woman with essential hypertension pregnancy causes an increase of blood pressure and an aggravation of all the hypertensive symptoms Dill and Erickson found that constriction of the renal arteries in pregnant dogs causes an eclampsia like syndrome but Foa and associates found that when rats made hypertensive by constriction of one renal artery become pregnant the blood pressure falls

Blood Pressure Hypertension is an almost constant symptom of eclampsia and preeclampsia Schwartz stated that he had never seen a case of eclampsia or preeclampsia without hypertension Seitz however found 13 per cent of his patients with a systolic pressure below 130 mm Hg He found the systolic pressure over 150 mm Hg in 64 of 98 instances of eclampsia and 30 of 35 instances of preeclampsia Hiess and Beckmann reported 13 cases with no elevation of blood pressure on repeated examinations Greenhill found the systolic blood pressure above 150 mm Hg in 70 of 78 cases

Heynemann called attention to the marked lability of the blood pressure in eclampsia A temporary hypertension is easily over looked especially when the patient is first seen late in the illness Severe cases particularly patients in coma are apt to show a fall of blood pressure In 8 of 56 cases which he studied carefully Heynemann never found the systolic pressure above 135 mm Hg but he stated that the usual pressure was 150 to 180 mm Hg and that he had not seen a patient with pronounced preeclamptic symp-

impression is that the prognosis is worse with severe hypertension

In our cases which were evidently severe the blood pressure was recorded in 57 of the 59 The systolic pressure was 150 mm Hg or

higher at some time in 51 cases and in 23 it was 200 mm Hg or higher In 2 cases it was between 140 and 150 mm Hg In No 30-318 a pressure of 138/80 was recorded one week before death In No 44 1794 the blood pressure was recorded before delivery and before the onset of eclampsia Likewise in No 48-722 the blood pressure was taken when there were no symptoms of eclampsia No 33-141 is possibly not eclampsia since there were no lesions in the kidneys and the liver showed only focal necroses There were no preeclamptic symptoms but the patient developed convulsions during labor and died before delivery

Pathological Anatomy of Eclampsia *The Brain* A few observers have reported petechial hemorrhages and microscopic areas of necrosis in the brain Sometimes a definite encephalitis is found with perivascular collections of lymphocytes and areas of demyelination The coma and convulsions may often be explained on the basis of the lesions in the brain

The Liver The characteristic gross lesions are irregular areas of hemorrhage associated with necrosis or atrophy of the liver cords (hemorrhagic necroses) and small areas of anemic necrosis The hemorrhages are often subcapsular but may be found anywhere within the organ Macroscopic lesions (hemorrhagic necroses) are absent in from one fourth to one third of the cases They were absent in 22 of our 58 cases in which the liver was examined Microscopic study often reveals small necrotic foci in livers that show no gross lesions but only the gross lesions are of diagnostic value Thromboses of small hepatic arteries or veins are usually found in relation with the necroses but it is not established that the thromboses are primary they may be a result of the necrosis The necrosis of the liver is occasionally extensive enough to produce jaundice

The Kidneys —The kidneys are affected in practically all cases of eclampsia The macroscopic changes are constant and easily recognized Apart from the cortical necroses which will be described separately there is an appearance of extreme cloudy swelling The kidneys are usually enlarged In 41 of our 58 cases the combined weight was 300 gm or more and in 16 cases 400 gm or above The cortices are always cloudy and opaque This appearance is constant but not distinctive of eclampsia since it occurs in a wide variety of toxic and infectious processes

On microscopic examination the tubules usually show precipitated protein and a few casts in their lumens but retrogressive changes in the tubular epithelium are inconspicuous There is no serious tubular injury

The Glomerular Lesions Pels-Leusden 1895 noted that the glomeruli are enlarged and contain only a little blood He interpreted the lesion as glomerulonephritis Lohlein 1918 gave the first clear description of the characteristic glomerular lesion in eclampsia He noted thickening of the walls of the glomerular

eclampsia except during an eclamptic crisis when it is notably reduced

We may conclude that there is often a slight and rarely a severe nitrogen retention in eclampsia but that apart from the cases of cortical necrosis there is no serious damage to the kidneys

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Mudaliar and associates did not find a cons...
le... of the blood pressure and the mortality but the general
...ertension
was
g or

some increase of endothelial nuclei in many cases and sometimes a rather striking increase is noted but it is never pronounced enough to warrant a diagnosis of acute glomerulonephritis The endothelial cells lie internal to the thickened basement membrane and contribute to the obstruction of the capillaries The glomerular lesions are present in 57 of our 59 cases but they are more pronounced and more easily recognized in some than in others The narrowing of the capillaries is recognized more easily than the thickening of the basement membranes The glomerular lesions are



FIG 5 Glomerulus from a case of eclampsia Mallory Heidenhain stain Note narrow capillary lumina thick basement membrane and swollen glomerular epithelium Photomicrograph

very prominent (Grade 3) in 29 fairly conspicuous (Grade 2) in 19 and slight (Grade 1) in 9 cases In two instances there were no glomerular changes Grades 3 and 2 are easily recognized in hematoxylin eosin preparatic
tions stained by the
Grade 1 lesion is insuffi

capillaries decrease of erythrocytes swelling of the glomerular epithelium and a slight increase of intracapillary cells He stated that the les on re on bl [illegible]

of some of the tufts No increase of glomerular nuclei was found as a rule but there were some exceptions He considered the glomerular lesion peculiar to eclampsia and called it glomerulonephrosis He interpreted it as a degenerative change best explained by the toxic theory of eclampsia



Fig 54 Glomerulus f om a ca e of eclamps a The glomerular cap llar es have very small lumina Lobulations are d st nct and tl ere s no notable ncrease of nucle Hematoxyl n eos n Photom crograpl

[illegible] and under low magni

examined under high magnification reveal the nature of the lesion The most striking change is extreme narrowing of the capillary lumens their opposite walls often being in contact (Fig 55) The narrowing is brought about by two processes viz thickening of the capillary basement membranes and swelling of the glomerular epithelial cells which surround the capillaries Practically all of the erythrocytes have been forced out of the capillaries There is

Tab e 36 Ec amps and Preecl mps a *Cont nued*

A topsy no	Age	Gravida	Dura n of pr gnancy m	Dura on of symptom	Albuminuria	Spec fi gravi urine	Ed ma	Blood pressure mm Hg	B ood u ea nitrog n mg pe cen	Convuls ns	H morrhagic necrosis li	W gh of kidn ys gm	Glomerular lesi ns	Comm n
32 794	37	8	0	2 mo		0 8	2	59/92		+	+	250	2	Placenta previa
32- 9 4	29	7	5	6 da.	0	0"0	3	5 /96	4	+	+	360	3	O guria
					4	042		20 05						
33-44	38		0	3 da.	8	040	0	38/?		0		5 5	3	
								6 m						
								200/7						
33 4	2	1	9	0	3	032		6/86	0	+	0	400	0	
33-749	30		6	3 da.		0 6	3	58/96	5	0	+	205	3	
33-905	36	1	9	2 mo	4	0 0	0	260 0	23	+	+	80	3	Ec amp s a 6 h and 7 h preg nanc
									m					
33- 3 9	3		0	3 hr	4	030	0	240 60		+	+	450	2	
33 586	38	1	7	8 da.	4	0 4		80 00	5 9	0	0	5	3	
									35 4			on		
33- 93	4	5	8	5 h	4		0	23 0			+	330	2	
34- 8	33	2	0	2 da.	2	009	0	0/90		0	0	230		
34 5	42	6	8	m	1		3	60 0	6	0	0	64	2	
								230 0						
35-50	36	1	0	4 da	3			204 6		+	0	3	2	
35 9 3	28		0	6 wk	1	0 3		60 0	9	0	0	500	3	
					4	030		25 00						
36-44	40	4	7	2 wk	4	0.5	2	220 30				470	2	
36-2070	38	3	0	5 wk	3	0 2	0	8	9 9	0		598	2	
36-2 54	33	3	8		4		0	98 24	23 8		+	375	3	
3 -9 5	30	2	6 5	2 wk	4		0	2 0 0		0	+	3 5	2	
3 009	30		7 5	9 da.	3	0 9	2	222 60	6 8	+		225	3	
39-50	4	2	9	6 da.	4			60	29 4	+	0	339	3	
								70 40	5 8					
39-55	6	1	9	3 wk							0	92	3	F und d ad
39-8.3	2		0	mo	3	0?0	2	38 94	4	+		343	3	
								70 30						
39 34	40	5	9	6 mo	0	0 8		6/90	NPN	0	0	350		
					4			6 m	"0					
								00 20						
39- 90	32	1	8 5	25 da.	4		0	2 0 20	N m	+	0	400		
39-2035	2		8	0 da.	4		0	00		0	0	350		
40- 29	39	5	0	6 mo				00 20	00	0	0	340	2	
40-738	2		9	29 hr	4	030		70 6	34	+	+	29	3	
40- 385	3	1	0	da.			0	2 2/160		0		350		
4 -579	22	2	0	5 wk	4	.030	3	154 8	24 8	+	0	500	2	preg a y norma
								170 5	to 9					
4 053	34		6	3 wk.	4	1 020	0	50 85		+	0	350	2	4 h. 2 6 glob 2 good p ur
								70 9						
4 705	4	7	0	da.	4			30 34		0		3 0	3	Diabe es many ars
								3 wks.						
								204 2						
4 0 2	20	1	0	1 wk	3		0	20 80	53 7	0		325	2	Di be acid
								(3 da.						
								90 00						
4 60			0	2 wk	4			90	6		0	5 0	0	Py ne hr is
								6/72	4					
4 4	26		9	2 d	0			65			0	2	3	P te d
					4		0	64 6						
4 79		3		2 h	4		0	2 80		+		43	2	P partum
5- 90	4		8	0 da				h		0		R 50 L 5		Pr mary hyper n
4 8	30		0	d				30		+		70	3	
46- 5	20		8	3 wk.	4		3	40		+	+	70	3	Rheumati d ar
46-722	8		0	0				30 70			0	3	3	O a d ects

The ntens y of the g omeru a les ons nd a d by nume a s 1 2 and 3 M Mul para

17

One patient (No 28-123) had primary hypertension for fourteen years preceding her death There were no convulsions and no changes in the liver were found at postmortem, but the characteristic glomerular lesions were present In two instances the eclampsia was associated with severe diabetes One patient (46-1315) had recurrent acute rheumatic endocarditis another (44 1741) was having severe symptoms from a patent ductus arteriosus and one (48-722) was having symptoms from old mitral and aortic valve defects

The glomerular lesions are useful in establishing the diagnosis of eclampsia since they are frequently present in the absence of hemorrhagic necrosis of the liver In one instance (No 39-551) the patient was found dead and the diagnosis of eclampsia was based entirely on the glomerular lesions

The character of the glomerular lesions suggests that they are of a degenerative nature They have none of the features of known inflammatory reactions It is highly improbable that such a change could result from anemia occasioned by spasm of the afferent arterioles since the glomeruli connected with sclerotic narrowed

TABLE 36 —ECLAMPSIA AND PREËCLAMPSIA

Autopsy no	Age	Gravida	Duration of pregnancy mo	Duration of symptoms	Albuminuria	Specific gravity of urine	Edema	Blood pressure mm Hg	Blood urea nitrogen mg per cent	Convulsions	Hemorrhagic necrosis, liver	Weight of kidneys gm	Glomerular lesions	Comment
21-477	35		9+				0	High	—	+	+	295	3	Jaundice found dead
25 120	31	1	5 5	5 wk	4	1 034	1	125 80 (2 wks)	27	+	+	300	2	Oliguria jaundice
25 289	41	3	8	3 da.	4	1 037	0	184/90 165 115	—	+	+	390	2	Eclampsia 7 yrs before old glomerular lesion
25 771	40	1	8 5	3 mo +	4	—	2	2 6 150	—	+	+	3 5	3	Retinitis blood
26 145	18	1	6 5	8 da	4	1.018	1	148/98	24	+	0	245	2	Purulent ethmoiditis
26-283	17	1	9+	1 da +	4		0	150 110 180/?	—	+	+	300	1	Oliguria
26 725	37	1	6 5	1 da.	4	1 016	0	195/130	22 0	+	+	375	3	Jaundice
26 965	40	M	9+	2 mo	3	—	0	2 0/ ?	—	+	+	—	3	Oliguria
28 123	38	2	8	?	4	1 030	1	215/120	23	0	0	275	3	
28 383	18	1	9+	2 da	4	—	1	188/120	—	+	+	300	3	
28 5 6	38	1	7	2 da.	4		0	230/110	17 7	+	+	280	2	Oliguria
28-533	25	1	10	5 da.	4	—	2	160/ ?	—	+	0	370	3	
28 1228	39	7	9+	1 da.	—		1		—	—	+	405	3	
30-318	28		9	—	0 4	—	0	138/80 (1 wk)	—	—	+	265	3	Found dead
30 1760	27	1	9+	1 wk	3	—	1	170/108	—	0	0	400	3	
31 708	19	—	9 5	1 mo +	4	1 031	3	150/100	14	+	+	450	2	
31-476	18	1	10	1 wk	4	—	1 1 3	200 ? 150 100		+	+	490	1	Oliguria
31 1953	45	2	10	—	4		0	130/?	34	0	+	390	3	
31 1983	24	1	10	6 da	1—	—	1	150/110	—	+	0	270	1	Gained 35 pounds
31 2091	31	M	10	3 wk +	4	—	1	230 160	—	+	+	350	1	Bacterial endocarditis
32-300	29	3	10	3 wk	4		1	165/96 190/95		+	+	317	3	

remained stationary for some time but disappeared after recovery The part of the vessel distal to the contracture is dilated This is convincing direct evidence of the presence of functional arteriolar spasm in eclampsia

Wagener confirmed and extended the observations of Mylius He found that the spasm may affect any or all of the branches of the central artery and that the contraction varies in degree and situation from day to day Later as the contractions become more fixed cotton wool patches and hemorrhages may appear in the retina and finally a diffuse retinitis may develop Spastic lesions are found in about 70 per cent of cases of toxemia and in about 60 per cent they disappear after labor Organic lesions of the retinal arterioles persist after labor and are usually accompanied by persistent hypertension

Kinukawa described subretinal accumulations of fluid in two retinæ which he studied microscopically

first twenty four hours after labor The symptoms are not relieved by intrauterine death of the fetus The fact that eclampsia occurs frequently with hydatiform moles is convincing evidence that the causative agent is in placental tissue

The second established fact is that there are spastic contractions of the arterioles in eclampsia The tetanic contractions are readily seen in the retina and it may be safely inferred that they are generalized

substance which acts upon the arteriolar musculature either directly or through the intermediation of the sympathetic nerves and (2) that a toxic substance is formed in the placenta possibly in the necrotic tissue of infarcts and that this product injures the glomeruli narrowing the glomerular capillaries and producing some interference with the renal circulation The placental poison need not be a pressor substance if it acts by producing renal injury

The After Effects of Eclampsia and Preeclampsia There is a widespread opinion that a frequent sequel of toxemia of pregnancy is some form of chronic nephritis or permanent hypertension Most of the writers who report chronic nephritis following toxemia do not specify the type of nephritis and usually base the diagnosis on the presence of hypertension or albuminuria Since there is no evidence that chronic glomerulonephritis is causally related to toxemia the problem becomes whether permanent hypertension is caused by the toxemia of pregnancy

arterioles become smaller not larger The most plausible explanation of the glomerular lesions is that they are the effect of a toxic substance circulating in the blood

Symmetrical Necrosis of the Cortices of the Kidneys —The first case of this kind was described by Bradford and Lawrence in 1898 and since that time a number of similar cases have been reported (see references) *The outstanding clinical features are preeclamptic symptoms with or without convulsions followed by severe oliguria or anuria and ending in death within a few days* It has been observed in both multiparæ and primiparæ and seems unrelated to age Definite preeclamptic symptoms are described in every case but about half of the patients have no convulsions The stage of gestation varies from three and a half months to full term The scanty urine contains blood albumin and casts The blood metabolites increase to a uremic level before death but typical uremic symptoms are commonly absent

The kidneys in every case are similar There is almost complete *necrosis of the cortices of both kidneys but usually a thin zone of* intact tubules may be found immediately adjacent to the medulla and a few tubules adjacent to the capsule are not necrotic The large branches of the renal arteries are unaffected but there is thrombosis of *all the small arteries and arterioles within the cortex* The necrosis of the cortex is clearly due to occlusion of all the small renal arteries since there are intact tubules under the capsule and adjacent to the medulla where there is some collateral circulation If the injury were due to some circulating toxic substance it would not spare these tubules The occlusion of the arteries may be due to a primary thrombosis but it seems more probable that it is caused by prolonged severe vasospasm There is a demonstrable vasospasm in the retinal arterioles

Similar lesions are sometimes found in males and 3 such cases males have come under my observation

The Placenta A few small placental *infarcts are found in about*

infarcts are due to thrombosis of placental arteries

that necrotic placental tissue is the source of a toxic substance that causes eclampsia Hunt and associates agree with this interpretation

The Retina —Mylius 1929 observed the retinal arteries in eclampsia and preeclampsia and noted tetanic contractions which

nephritis but 4 of the 5 had nephritis before the eclamptic pregnancy

Nevermann, 1927, reexamined 60 patients, one to twenty-three years after eclampsia Thirty-seven were studied more than ten years after the eclampsia Twenty-seven were entirely normal but the others had various complaints such as headache, poor memory, visual disturbances and edema of the legs Eight women had hypertension (140 to 170 mm Hg) Three had albumin and casts (*a*) one year after eclampsia, trace of albumin, blood pressure 118 mm Hg, (*b*) eclampsia in 1903 and again in 1905, albuminuria on dismissal each time, since 1905 seven abortions and premature labors in 1925, blood pressure 170 mm Hg large amount of albumin, (*c*) eclampsia in 1921, mild preeclampsia with abortion in 1925 (albumin), normal in 1926 There was only one patient with a persistent renal lesion

Peckham, 1929 found 17 (23 per cent) of 77 women with chronic nephritis on reexamination one year after eclampsia Nephritis developed somewhat oftener in those who were albumin-free at the end of three weeks than in those who had albuminuria at that time Peckham did not explain the criteria on which his diagnosis of nephritis was based

Schmechel 1929, in a large experience with eclampsia, knew of only one patient who developed chronic renal disease He thought that this patient probably had renal disease before pregnancy

Kobes, 1930 found that 19 of 32 eclamptics had albuminuria at the end of the third week after the attack Reexamination of the 32 women from three to eighty-five months later showed only 3 with albuminuria Fourteen of 19 preeclamptics had abnormal urine when reexamined but 13 of these had a history of renal disease prior to pregnancy Two women of this group had evidence of contracted kidneys

Seitz, 1930, found 78 eclamptics all entirely well at the end of eight weeks The preeclamptics (17 in number) showed a little slower healing A few were not normal after fourteen weeks

Breaky, 1932, traced 115 eclamptics and 218 women who had had normal pregnancies Using 150 mm Hg as the standard, 26 5 per cent of the eclamptics and 21 6 per cent of the controls had hypertension Albuminuria was found in 6 38 per cent of the eclamptics and 2 per cent of the controls Two definite cases of chronic nephritis developed in the eclamptics

McKelvey and McMahon, 1935, concluded that the toxemias of [illegible] Irwing, [illegible]

[illegible] und that 43 per cent of 3000 women after eclampsia and preeclampsia were reported to have a systolic pressure over 140 mm Hg Fourteen per cent of 930 had persistent albuminuria They believe that 20 to 40 per cent of women are left with permanent hypertension

Koblanck 1894 reexamined 77 women who had had eclampsia (time of recheck not given) 59 7 per cent had no albumin 10 9 per cent had only a trace of albumin 15 4 per cent had catarrh of the urinary tract and 6 5 per cent had nephritis

Meyer Wirz 1904 found that the great majority of eclamptics were free from albumin on dismissal from the hospital Zangemeister 1913 found 7 per cent of eclamptics with residual chronic nephritis and attributed the majority to the attack of eclampsia

Baisch 1913 traced 110 women who had had an attack of eclampsia (60 cases) or severe preeclampsia (50 cases) Of these 110 patients 9 were dead and 11 were permanent invalids Only 40 per cent were entirely well No information was given as to the cause of death or invalidism and no evidence of renal disease was presented

Wolf and Zade found 2 out of 23 eclamptics whom they reexamined some years later with evidence of chronic nephritis (hypertension) Neither patient had albuminuria upon dismissal after the attack of eclampsia

Sachs 1918 found 81 of 87 eclamptics entirely well on reexamination some years later Four were dead and 2 had signs of chronic nephritis

Hussy 1921 did not see any instance of chronic nephritis after eclampsia

Breuning 1924 in a report of 88 cases of eclampsia stated that 88 per cent of those who survived were free from albumin on dismissal from the hospital

Heynemann 1924 traced 45 cases of eclampsia and 7 of severe preeclampsia He found albuminuria or hypertension not infrequently on dismissal and on later examinations He interpreted the abnormal findings as *delayed healing* or as *vascular disease* resulting from eclampsia

Zondek and Jacobowitz 1924 reexamined 38 patients who had had eclampsia or preeclampsia one to seven years later There was one case of *chronic nephritis* which they believe was present before

renal function

Greenhill 1926 followed 60 cases of eclampsia and found 55 with normal blood pressure and normal urine Five *developed chronic*

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after a toxemia They attribute the permanent hypertension to a persistence of the glomerular lesions of acute eclampsia Seven women who were known to have had a previous toxemia and who died of other causes later all showed thickening of the capillary basement membranes

Dieckmann 1939 does not believe that toxemias of *pregnancy* cause permanent renal damage He believes that repetition of toxemia in a subsequent pregnancy suggests primary vascular renal *disease*

Weiss 1940 stated that in his group of toxemias about one-third of the patients had hypertension before pregnancy but sustained hypertension follows toxemia in about one-third of the patients who

hypertension which follows a large proportion of the toxemias of pregnancy is not the result of the toxemia but that toxemia occurs for the most part in women who have a tendency to hypertensive disease

In a previous paper 1932 I reported the histology of the kidneys in a patient who died seven years after an attack of eclampsia A great many glomeruli show focal scars which were interpreted as the outcome of the acute eclamptic lesion This observation how

found no evidence of damage from the first attack

It is clear from the literature that the experience of different observers has not been uniform It is also highly probable that the diagnosis of chronic nephritis usually refers to hypertensive vascular disease There seems no doubt that an undetermined percentage of women who have had toxemia of pregnancy develop hypertension later on Our problem therefore is to determine whether this hypertension is a result of the previous toxemia or a manifestation of primary hypertensive disease unrelated to toxemia The evidence appears definitely in favor of the latter interpretation About 50 per cent of women past middle life have hypertension (Wetherby) It is to be noted also that Breaky found hypertension almost as frequently after normal pregnancy as after eclampsia Many of the women who subsequently developed hypertension following toxemia were normal on dismissal from the hospital The vascular and renal lesions in hypertension after toxemia are not different from those found in cases of hypertension in males or in females who have not had toxemia

The only type of case which presents any difficulty to the above interpretation is the infrequent one in which the patient has a normal blood pressure before pregnancy develops an hypertensive toxemia and maintains a persistent hypertension from that time on

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CHAPTER VII

TUBULAR DISEASES

PRIMARY disease of the renal tubules is of two anatomical types degenerative and obstructive In the former the tubules are injured by a circulating poisonous substance to such a degree that their functions are interfered with in the latter their lumens are blocked by casts or by substances precipitated from the urine Mild tubular injury is found in nearly all acute infections and toxic processes but clinical tubular disease is rare in comparison with other forms of clinical renal disease

Tubular diseases are usually called nephroses but this term no longer has an exact meaning Lipoid nephrosis is a glomerular disease amyloid nephrosis is chiefly glomerular and chemical nephrosis is tubular

The tubular diseases will be discussed as far as possible on an etiological basis It will be pointed out to what extent each type is degenerative or obstructive

1 **Chemical Poisons** A number of chemical poisons exert a selective action on the kidneys and all of them injure the tubules much more than the glomeruli Many substances have been used experimentally to produce nephritis those most frequently employed being uranium nitrate mercuric chloride and potassium bichromate All experimental nephritides produced by chemicals are tubular diseases In clinical experience mercuric chloride is responsible for uremia much more frequently than any other simple chemical poison but rarely other poisons are responsible

Mercuric Chloride —There is usually a history that the poison has been taken by mouth accidentally or with suicidal intent but fatal poisoning has resulted from vaginal douches and skin lotions

The initial toxic symptoms are epigastric pain nausea and vomiting The outcome depends largely upon the amount of poison ingested but patients may recover after taking a large amount if the poison is largely removed by vomiting or by prompt gastric lavage If gastric lavage is delayed for more than one hour very little of the drug can be removed

About one-half of those who develop toxic symptoms die either of shock or uremia Those who die during the first twenty four hours show little evidence of renal damage but those who die after that time always show severely damaged kidneys and death is due partly or entirely to uremia

In cases which terminate fatally oliguria usually develops during the first twenty four hours and is soon followed by anuria The scanty urine contains a trace to a large amount of albumin The

blood urea rises rapidly to uremic levels (Table 37) After several days of anuria diuresis may set in even in amounts as large as 1000 cc daily but the urine is of very low specific gravity and the blood urea continues to increase except in those patients who recover

TABLE 37 —TUBULAR DISEASE CAUSED BY MERCURIC CHLORIDE

Autopsy No	Age	Sex	Duration	Albuminuria	Edema	Blood pressure	Urea nitrogen mg per 100 cc	Urine	Weight of kidneys gm	Histology	
										Necrotic tubules *	Low dark nongranular cells
20 382	24	F	9 da	1	0			?	370	0	+
21 362	14	F	12 da		t	104 50	124	Oliguria da Anuria	360	0	+
25 81	37	F	7 h						2	0	0
28-994	26	F	16 da	4 1	0	26 80 64	20 62	Daily 1030 cc	370 abscesses	0	+
29 532	29	F	0 da	1	1	0/70		Severe oliguria	725	0	+
30-216	34	F	5 da	1	0	130/90			29?	+	0
30-1578	49	M	8 da	0	0		22 8		534	0	+
34 1080	45	F	7 da		0			Severe oliguria	350	+	0
35 2084	81	M	2 da +	1	0		09	Severe oliguria	334	+	0
36 1093	34	F	7 da		0	S elevation	89	Anuria	3	+	0
38 1855	21	F	11 da	2	Eyelids	120 70	14 102	Anuria Oliguria	500	0	+
4 1028	29	F	3 da		0				398	+	0
44-4	6	F	7 wk	3	Face	110 90	2 4 0	No oliguria sp gravity 010	470	0	+
4 -4 9	27	F	11 da	?	0	3 72	119	Oliguria sp gravity 0 0	47	+	0
4 373	45	M	1 da		0	90		Anuria	305	0	0
47-4	49	F	7 da	2	0	11 /78	30 11	Oliguria	300	+	0
47 19	43	M	5 da	—	0			Anuria	453	+	0
47 237	67	F	a few hours	—	0		—	Anuria	24	0	0

Edema is usually absent but there may be a small amount especially about the face Severe edema rarely occurs unless the patient has been given large amounts of fluid The blood pressure usually remains at a normal level but it may become moderately elevated during the period of anuria

The kidneys are usually only moderately enlarged but sometimes the combined weight is over 500 gm On section the cortices are pale and cloudy The microscopic structure varies with the period of survival When death occurs within a few hours the histological structure is normal When the period of survival is only a few days the tubules are filled with coarse fragments of necrotic epithelium (Fig 56) On preliminary study the tubular epithelium appears to be entirely destroyed but careful observation reveals that a thin basal portion of most of the cells is intact This persistent layer of cytoplasm contains the nuclei

After several days have elapsed the appearances are such as shown in Figure 57 The necrotic debris has been removed and the persistent basal portions of the cells are clearly visible In many places there is practically no cytoplasm remaining

Mercuric chloride as well as uranium nitrate injures only the proximal tubules The distal tubules and the glomeruli are unaffected *The selective action of these poisons on the proximal renal tubules is due to their concentration in this segment* Sollmann

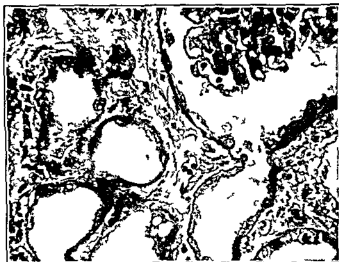


Fig 56 —Tubular disease from mercuric chloride poisoning Death three days after ingestion of the poison The tubules are filled with débris from necrotic epithelial cells Photomicrograph

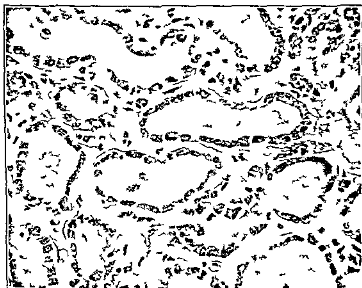
found the concentration of mercury in the kidneys much greater than in any other organ When one ureter of an animal is ligatured injection of mercuric chloride or uranium nitrate does not damage
... hal le that in
s formed
rate but

allow it to diffuse back into the blood stream

Those persons who die after the first week of which there are



Γ 57 Tubu a d e e from me u lo de po on ng Dea about one w ek af e ng s o of the po on T e n ro po on. of t e el a e been washed away A n basal po n o e em T e g om ru u s ows no hanges Pho om og aph



F G 58 Ti bu d e f m me u h de po son ng D a h from urem a two weeks af r nge on o he po on The eg n a d e the um s da k and non g anul P otom rograph

liver

The following four cases of carbon tetrachloride poisoning came under our observation

(a) 44–811 A female age unknown amount of carbon Vomiting Anuria Delirium Fatty liver with central necrosi

Severe oliguria Lived 10 day Blood pressure 144 100 mm Hg No

(d) 45–703 A female aged orty carbon tetrachloride for

vincing

REFFRENCFS

glycol)
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Uranium Nitrate.—This chemical has been used extensively to produce renal lesions in animals. It causes necrosis of the proximal tubules. Like mercuric chloride it produces its effect by being concentrated in the tubules since ligature of the ureter protects the kidney from injury.

Racemic Tartaric Acid.—When an animal is injected with racemic tartaric acid a severe hydropic degeneration of the proximal tubules results. Ligature of the ureter does not protect the kidney from injury. The hydropic lesion may heal but it often progresses to necrosis and the animal dies of uremia.

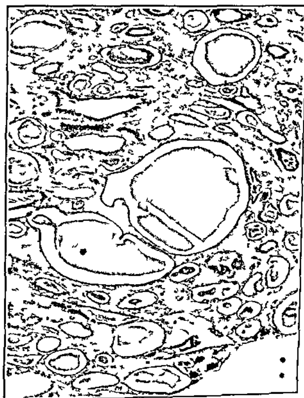
Sucrose.—In 1933 Helmholz found that when rabbits are injected with large doses of 20 per cent sucrose they develop severe hydropic changes in the renal tubules. The lesion reaches its maximum in twenty-four to forty-eight hours and then gradually recedes. Hypertonic solutions of sucrose are frequently used clinically to produce diuresis and similar renal lesions have since been repeatedly observed in human beings injected with sucrose shortly before death. In histological sections the lesion appears to be very severe (Fig. 9) but there is only a temporary functional disturbance and uremia never results. Apparently the severe hydropic change caused by sucrose does not result in permanent renal damage. Hypertonic solutions of dextrose do not produce any changes in the tubules (Lindberg, *et al.*). Wilmer found that sucrose, unlike uranium nitrate and mercuric chloride, produces the same degree of injury to the tubules of a hydronephrotic kidney as to those of the normal kidney.

Sulfa Drugs.—Our experience with fatal poisoning from sulfa drugs is shown in Table 38.

TABLE 38.—RENAL INJURY FROM SULFA DRUGS

Autopsy No.	Age	Sex	Sulfa drug	Duration of illness	Albuminuria	Edema	Urine	Blood pressure	Weight of kidneys	Hydropic tubules	Obstruction by crystals	Urea nitrogen mg. per cent
A	77	M	-pyridine -thiazole	16 da.	—	0	Oliguria	—	—	0	3	102
42-388	47	F	thiazole	8 da.	3	1	Oliguria Anuria	84/70	575	0	2	145
43-2154	50	F		8 da.	1	1	Oliguria Anuria	—	560	3	0	64
47-442	13	M		5 wk.	1	0	Oliguria Anuria	130/70	560	0	3	135
44-549	67	M	-diazine	10 da.	2	0	—	—	475	3	0	81
44-569	70	M		7 da.	1−	0	Oliguria Anuria	—	522	0	0	—
45-57	76	M	"	2 wk.	0	3	Oliguria Anuria	116/72	340	1	0	63
45-225	73	F	"	4 da.	—	0	Oliguria	60/50	338	2	0	88
46-692	64	M		4 da.	1	0	Oliguria	—	323	0	2	79
48-584	50	M		—	3−	0	Anuria	130/70	430	0	0	53
48-2516	60	F		9 da.	—	3	—	144/72	400	3	0	86

When sulfa drugs are given in such amounts as to produce a high concentration in the blood they are present in corresponding amounts in the glomerular filtrate and in the normal process of concentration in the tubules they may precipitate out in crystalline form The crystals may be washed into the pelvis where they traumatize the mucosa and cause hematuria and they may accumulate in sufficient quantity to obstruct the ureters Occasionally they obstruct the collecting tubules (Fig 60)



The following case from our autopsy records illustrates this lesion

CASE A Table 38 A male aged seventy seven years ... 13 On the first post... en fairly large d... es of ... d 15 after which only ... urred and sulfathiazol ... getting a satisfactory

much amorphous material containing sulfathiazole crystals was removed However the diuresis was never more than 325 cc daily, the blood urea continued to rise and the patient died of uremia on Dec 29

The blood urea nitrogen was 6 7 mg per cent on Nov 26, 22 4 on Dec 11, 62 on Dec 27, and 102 on Dec 28

The blood sulfathiazole was 16 mg per cent on Dec 23, 15 8 on Dec 26 39 8 on Dec 27 and 43 5 on Dec 28

In 5 of our cases (Table 38) anuria and uremia were due entirely to tubular injury and there was no accumulation of crystals in the tubules The following case is illustrative of this lesion



Fig 61 —41-2154 Anuria from sulfathiazole Marked hydropic degeneration of the proximal tubules Photomicrograph

43-2154 (Table 38) A woman aged fifty years was admitted to the hospital on Nov 8 wi ... she had been given a ... preceding forty eight ... cent No urine was

tubules and pelves is a low diuresis but the concentration in the blood is also important When the blood level is not excessively high and the fluid intake is sufficient to give a daily diuresis of 1500 cc or more there is little danger of precipitation

Climenko and associates found that monkeys tolerate a much higher blood concentration of a sulfa drug without renal complications when the urine is kept alkaline by administration of large amounts of sodium bicarbonate The sulfa drugs and their acetylated derivatives are many times more soluble in alkaline than in acid mediums Fox and associates recommend that bicarbonate be given to keep the pH of the urine about 7 5

A high fluid intake with sodium bicarbonate will prevent precipitation of a sulfa drug in the urinary tract, but we do not know how to prevent injury of the tubules Apparently sulfa drugs are toxic to certain individuals

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man hemolysis of the donor's cells occurs also when the donor and the recipient belong to incompatible blood groups. When a person is transfused with incompatible blood a severe reaction usually develops during or shortly after the transfusion. There is commonly a chill, fever, sweating and signs of circulatory collapse. The erythrocytes from the donor are hemolyzed causing hemoglobinemia and hemoglobin escapes into the urine when the amount in the blood exceeds the renal threshold.

A few patients die within a few days after the transfusion reaction with signs of circulatory collapse, and others develop oliguria within twenty-four hours.

The oliguria may persist a few days and then be followed by a good diuresis and recovery, but it may progress to anuria and uremia.

The fourteen cases which we have studied are summarized in Table 39.

TABLE 39.—TRANSFUSION KIDNEYS

Autopsy No	Age	Sex	Amount of blood	Duration of life, days	Urea nitrogen	Weight of kidneys, gm	Hydrope degenerat	Casts	Comment
34-1183	29	F	—	20	145	455	0	4	early tubular atrophy oliguria 3
39-1644	55	M	—	10	—	460	3	3	oliguria 3
40-871	53	M	—	7	75	500	0	4	oliguria 3
40-1944	67	M	None	12	115	485	0	4	prostatectomy irrigation with water
42-119	64	M	—		100	405	3	3	
42-634	71	M	—	2	69	510	0	3	jaundice
43-1101	50	M	—	4	—	415	0	4	anuria
45-621	31	F	700 cc	10	54	500	3	1	oliguria followed by good diuresis
46-721	68	M	None	12	109	450	0	3	prostatectomy irrigation with water
46-1752	74	M	750 cc	12	101	345	0	4	
47-1172	51	M	1500 cc	15	high	625	2	1	oliguria 3
47-1[illegible]51	74	F	2500 cc	5	90	290	3	1	
48-8	76	M	1000 cc	7	106	490	1	3	hemolysis during prostatectomy
48-1902	71	M	1000 cc	6	110	320	1	3	

The Kidneys.—The kidneys are usually greatly enlarged and on section the cortices are cloudy and increased in thickness. Microscopically there are always casts composed of some derivative of hemoglobin in the collecting and distal convoluted tubules and in the loops of Henle. The casts usually distend the tubules and seem to produce partial or complete obstruction but often the obstruction is obviously incomplete. Occasionally there is a moderate dilatation of some of the proximal tubules suggesting an obstruction in the lower part of the nephron. Often some degenerative changes are seen in the tubular epithelium at the site of the cast, and frequently

there is a cellular exudate surrounding the tubule containing the cast In five of our cases the large number of casts (Grade 4, Table 39) (Fig 62) seems an adequate cause of the renal insufficiency, and in six others (grade 3) they appear to be an important contributory factor However, in three cases (grade 1) the casts are too few in number to have played an important role



FIG 62 —Transfusion reaction showing extensive obstruction of tubules by precipitated hemoglobin Photomicrograph

Ayer and Gauld do not believe that the casts cause renal insufficiency since they found an equal number of casts in cases of deep jaundice without renal failure

Burwell and associates described the kidneys of a person who survived uremia following a transfusion and died three months later of serum hepatitis Their illustration shows wedge-shaped areas of tubular atrophy strongly suggesting permanent obstruction of groups of nephrons

To my knowledge no investigator has called attention to the marked hydropic degeneration of the proximal convoluted tubules that was found in some of our cases Definite hydropic degeneration

is present in 7 cases and in 4 it is severe (Fig 63). The cells are greatly enlarged and they are filled with irregular vacuoles. There is little doubt that this lesion may cause renal insufficiency. In the 3 cases in which casts are inconspicuous this lesion is prominent (Table 39). The distal tubules show only mild hydropic changes. The frequency and prominence of injury of the proximal tubules shows that the lesion in the transfusion kidney is by no means restricted to the lower part of the nephron as some investigators have claimed.



Fig 63 Transfusion reaction showing severe hydropic changes in the proximal convoluted tubules the distal segments and glomeruli being normal. Photomicrograph

The primary disturbance in uremia following blood transfusion is hemoglobinemia due to hemolysis of the donor's cells. But the source of the erythrocytes is not important since the same lesion may result from hemolysis of the patient's own erythrocytes as in blackwater fever and in transurethral prostatectomy. In prostatectomy the operative site is irrigated with water under pressure which enters the veins and hemolyses the erythrocytes. During the prostatectomy hemoglobinemia is often demonstrable and hemoglobin may

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the veins and hemolyses the erythrocytes During the prostatectomy hemoglobinemia is often demonstrable and hemoglobin may

accumulate in sufficient amounts to produce renal insufficiency and death (Creevy Landsteiner and Finch)

Baker and Dodds believed that casts do not form in the tubules unless the urine is acid but other investigators do not support this view De Navasquez was unable to confirm the work of Baker and Dodds and he also reported a patient who had an acid urine throughout an attack of paroxysmal hemoglobinuria without any disturbance of renal function Severe oliguria may also develop in the presence of an alkaline urine (De Navasquez) Yuile and associates obtained casts in rabbits only when the tubules were previously injured by temporary clamping of the artery or by sodium tartrate but they obtained more casts when the urine was acid

Lalich found that dehydration favors the accumulation of casts in the kidneys of rabbits This is presumably due to the greater concentration of the glomerular filtrate in the tubules

Several observers have noted a direct relation between the amount of blood transfused and the degree of renal injury (Flink) In so far as the renal insufficiency is due to casts one would expect this to be true

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injury to the proximal convoluted tubules has not been explained

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Bacterial Poisons In persons suffering from a severe infection of [illegible] only some protein in the urine but there is

Burns —Severe burns may cause oliguria or anuria from loss of plasma in the burned area The uremia which may result seems to be chiefly extrarenal in origin Baker in a study of 96 cases dead of burns found only 4 with renal lesions attributable to the burn

Miscellaneous Forms of Uremia —In Table 40 fifteen cases of uremia are listed which are due to injury or obstruction of the tubules Often the cause of the tubular injury is obscure In Nos 33 2051 and 42 114 there was a severe suppurative inflammation In No 43 38 there was severe obstructive jaundice with extensive obstruction by casts and hydropic degeneration

TABLE 40 MISCELLANEOUS FORMS OF UREMIA

Autopsy No	Age	Sex	Major disease	Albuminuria	Edema	Blood pressure	Urea nitrogen mg per cent	Weight of kidneys gm	Hydropic degeneration	Casts	Comment
33 2051	3[illegible]	F	Postoperative suppuration	3	0	Normal		370	3	1	[illegible]
35-483	24	F	Childbed fever 12 days		0	130 80	123	580	4	1	Oliguria
41 [illegible]04	3[illegible]	M	Severe oliguria 3 wk	3	2	Normal to 208 140	—	5[illegible]0	3	1	
41 2647	38	M	Severe diarrhea	[illegible]	1	144 72	16[illegible]	[illegible]65	0	0	Oliguria precipitate in tubules
41 84	66	M	Carcinoma of lung	0	0	156 90	102	650	0	0	Complete replacement by tumor
41 807	60	F	Cholecystitis	3	0	140 8[illegible] 1[illegible]/80	93 44	545	3	1	Oliguria jaundice
42 739	6 mo	F	Diarrhea vomiting		1		5	[illegible]0	0	4	Proximal tubules blocked by crystals
42 1066	10	F	Severe vomiting 2 wk	1	1	140/90	15[illegible]	350	0	1	Moderate atrophy
42 114	55	F	Postoperative suppuration	1	0	170 80	50 90	4[illegible]0	3	3	
43 38	68	F	Obstructive jaundice		0		54	500	2	4	Oliguria
45 438	16 mo	F	Severe vomiting sulfa drug		0			60	2	0	Oliguria
4[illegible] 17	76	M	Prostatectomy transfusion		0	130 80	190	39	1	1	
46 1637	55	F	Uremia	1	0	140 108	144	[illegible]0	2	0	
41 1481	1 mo	M	R[illegible] disease	1	3 0		14	51	0	0	Necrosis of pyramids
47 11[illegible]2	51	M	Acute pancreatitis	1	0		190	6[illegible]	3	0	

In No 35-483 there was a severe hydropic degeneration of unknown etiology (Fig 64)

In Nos 40 2047 42 739 42 1066 and 45-438 dehydration probably played an important role In 42 739 the dehydrated infant showed complete obstruction of all the proximal tubules by crystals which were not identified

In No 41-84 uremia was due to complete replacement of the kidneys by tumor

Fig 64 Severe tubular disease of unknown etiology 35-483 Table 40 Extreme hydropic degeneration of proximal tubules Distal segments (in center) and glomeruli normal Photomicrograph

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The Hepato renal Synd

diffuse cortical necrosis of
of the liver There was se
described the case of a boy 16 years of age who survived for eleven days following severe crushing of the liver There was oliguria which progressed to anuria and uremia The kidneys showed marked degenerative tubular lesions The authors attributed the tubular lesions to toxic substances liberated from the necrotic liver tissue

Schutz Helwig and Kuhn (1932) reported 4 cases of anuria and uremia following cholecystectomy They regarded their cases as examples of renal disease secondary to hepatic necrosis Patel 1936,

reproduced the hepato renal syndrome in rabbits by ligature of the hepatic artery or by traumatizing the liver

The hepato renal syndrome is extensively discussed in the literature and many of its features are still obscure but there is little doubt that necrosis of the liver sometimes brings about necrosis of the renal tubules and uremia

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Multiple Myeloma —Multiple myeloma occurs chiefly in elderly persons Fifty six of our 65 patients were over fifty years of age

sufficiency Albuminuria is found in the great majority especially in advanced stages of the disease but it varies greatly in intensity and at times may be completely absent

The protein in the urine may consist entirely of the Bence-Jones body entirely of serum protein or of a mixture of the two proteins The more careful investigations indicate that when the Bence-Jones protein is present it constitutes the greater part or all of the urinary protein The literature indicates that the Bence-Jones protein may be found in the urine at some time during the course of the disease in about two thirds of the cases

The Bence-Jones protein may be excreted by normal kidneys and its presence in the urine therefore does not indicate any renal lesion Serum albuminuria is attributable to minor glomerular lesions

weighing less than 200 gm had uremia

In 17 of the 27 patients with renal failure the renal insufficiency is clearly due to large numbers of casts which block the collecting tubules The casts block the tubules completely and are permanently lodged there Macrophages are often found invading the tubule and attacking the cast It is not known whether the casts are composed of Bence-Jones protein or serum globulin. In our cases no correlation could be established between the presence of casts and



FIG 65 —Contracted kidneys from a case of multiple myeloma with uremia The tubules are extensively obstructed by large firm casts and the segments proximal to the casts are markedly atrophic The glomeruli are unaffected Photomicrograph

the level of serum globulin or the presence of Bence-Jones protein in the urine Numerous casts were found in occasional cases in which the plasma globulin was not increased and no Bence-Jones protein was found in the urine

The effect of a cast is ultimately atrophy of the nephron proximal

zer, 1932 described such a case and interpreted it as a nephrotic

disuse atrophy because the nephron cannot perform its functions The glomeruli show no structural alterations but glomerular filtration must be suppressed

In rare instances renal insufficiency is due to accumulation of a

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PERLA D and HITNER I

The Crush Syndrome —Bywaters Beall and others have reported many instances of anuria and uremia following crushing injuries of *the extremities The patients were all air-raid victims whose ex*tremities had been severely compressed for several hours before they were rescued After release of the compression the limb be-

the specific gravity of the urine decreases and uremia develops Arterial pressure and serum potassium are increased About two-thirds of the patients die of uremia

A similar clinical picture may develop when the arterial supply to an extremity is occluded for several hours

reaction about the affected tubules The casts are composed of myoglobin The authors did not mention any lesion of the proximal tubules

urine it causes the formation of myoglobin casts which may be numerous enough to produce uremia

Corcoran and Page made the interesting observation that when tourniquets are applied to the limbs of dogs that nearly obliterate arterial flow the renal blood flow is reduced to 20 per cent of normal In this condition of vasoconstrictive ischemia myoglobin which has little effect on a normal kidney is precipitated in the tubules The precipitation is favored by the oliguria and the acid urine

Myoglobinuria resulting from necrosis of muscles occurs in horses when they are put back to work after a rest period of several days on a high carbohydrate diet

Myoglobinuria occurs in man in chronic degenerative lesions of the voluntary muscles and it may lead to renal failure One such case came under our observation The patient had repeated attacks of muscle soreness following severe exercise associated with myoglobinuria In his last severe attack he died of uremia There was widespread patchy necrosis of the voluntary muscles There were only a few myoglobin casts in the distal and collecting tubules but there was a mild hydropic degeneration of all the proximal tubules There was much more injury to the upper than to the lower nephron

Trueta believes that the anuria of the crush syndrome is due to prolonged spasm of the renal arteries at the cortico-medullary junction which shunts the blood into the veins and causes anemia of the cortex

The evidence suggests that in the crush injury there is severe vasoconstriction of the renal arteries causing cortical ischemia The anoxia is the chief cause of the renal injury Oliguria and an acid urine develop and myoglobin casts obstruct many of the tubules

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MORISON[illegible] June

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injured tubules and an inflammatory reaction deve[illegible] them This explanation of [illegible] e and others and the lesion [illegible] osis' The present concept

of lower nephron nephrosis seems to be any renal lesion with casts or injury in the distal and collecting tubules and the loops of Henle Some of the authors believe that there is a primary injury of these segments others think they are merely obstructed by casts

Lucke has extended the concept to include the crush syndrome

tubular disease

There are serious objections to the concept of lower nephron nephrosis

(a) In a fairly high percentage of transfusion and sulfa drug kidneys there is a severe hydropic degeneration of the proximal tubules (Fig 60) and there may be very few casts In other words a fair proportion of these cases are chiefly lesions of the upper nephrons The advocates of lower nephron nephrosis have ignored the lesions in the proximal tubules or have attempted to explain them as a result of obstruction of the distal segments But obstruction of a tubule causes dilatation or atrophy in the proximal direction not hydropic degeneration

(b) The idea that there is a primary injury of the distal segments is not sound It is readily determined that the first event is

etiology and when a cast is permanently lodged in a tubule it frequently provokes an inflammatory reaction about the tubule This is characteristic of the casts of multiple myeloma

(c) The renal failure in tubular diseases is often more complex than the simple obstruction of tubules The number of casts is frequently not sufficient to explain renal failure There is usually vasoconstriction and anoxia of the cortex before the appearance of casts

The introduction of the term lower nephron nephrosis has been a disservice to renal pathology in that it has added confusion instead of clarity

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CHAPTER VIII

EXTRARENAL AZOTEMIA

EXTRARENAL azotemia may be defined as azotemia not due to primary renal disease There is renal failure but it is caused by extrarenal influences and not by structural changes within the kidneys It is not a circumscribed entity but a group of disturbances which produce a similar effect The essential features of the syndrome are oliguria azotemia and no renal lesion sufficient to explain the renal failure It is not sharply separable from definite tubular disease and many of the kidneys *from cases of extrarenal uremia* show hydropic changes in the cells of the proximal tubules which seem sufficient to have caused disturbances in their functions

*In hospitals where determinations of blood urea are made rou*tinely a fair percentage of the patients will show a moderate or severe azotemia during the last few days of life We have had the opportunity of studying the kidneys of 142 subjects with a terminal extrarenal uremia

An important and initial symptom is oliguria but the urine is never highly concentrated the specific gravity usually ranging from 1018 to 1024 In an oliguria occurring in a person with normal kidneys the specific gravity is much higher The low specific gravity of the urine is due in part to its very low content of sodium chloride

Zondek believes that extrarenal azotemia may usually be distinguished from true renal uremia by the concentrations of sodium chloride and urea in the urine In true renal uremia both sodium chloride and urea are very low (sodium chloride 0 2 to 0 4 per cent urea 0 3 to 0 9 per cent) In extrarenal azotemia sodium chloride is very low as in renal uremia but urea is high (4 per cent) He attributes the increased urea to endogenous breakdown of protein

In our group of 142 cases the terminal blood urea nitrogen as follows 50 to 59 mg per cent 19 60 to 79 37 80 to 99 27 100 to

A similar con

ids because of obstruction in the esophagus or stomach *those who refuse fluids* or those who are neglected We do not know whether the oliguria is due to decreased glomerular filtration or increased tubular reabsorp-

tion but after it has persisted for a few days it usually continues despite a high fluid intake Some permanent damage to the kidneys has been produced In our 15 cases the renal tubules were normal in 12 but 3 showed hydropic degeneration such as in shown in Figure 63

(*b*) Dehydration from intestinal obstruction vomiting (19 cases) This occurs most frequently from obstruction of the small intestine and paralytic ileus So much fluid is lost by vomiting or by accumulation in the intestines that the patient becomes dehydrated and oliguria ensues Chlorides are also lost excessively in the vomitus and the blood chloride falls well below the normal level For this reason the term hypochloremic uremia has been applied It was formerly believed that the loss of chloride caused retention of urea to maintain the osmotic pressure of the blood but Kerpel Fronius in a series of papers showed clearly that the azotemia is due to dehydration and not to low blood chloride Experimentally he produced hypochloremia without azotemia and showed that azotemia may be corrected by administration of water without salt Chlorides correct the alkalosis but not the azotemia Mach and associates found that in cirrhosis of the liver repeated drainage of the ascitic fluid reduced the blood chlorides as low as 300 mg per cent without producing any elevation of blood urea

In our 19 cases of azotemia from intestinal obstruction 2 show hydropic degeneration of the proximal tubules

(*c*) Dehydration from severe diarrhea (4 cases) This has been observed most frequently in the diarrheas of children and in Asiatic cholera A severe diarrhea produces a marked dehydration In 1 of our 4 cases there was hydropic degeneration of the proximal tubules

2 **Azotemia from Hemorrhage into the Gastrointestinal Tract —** [illegible]

[illegible] tributed by different investigators are as follows

(*a*) *Low Blood Pressure* —In those persons who develop shock following the hemorrhage the blood pressure may fall so low that renal blood flow and glomerular filtration are greatly reduced

(*b*) *Decreased Blood Volume* —A severe hemorrhage has a dehydrating effect Fluid is withdrawn from the tissues to restore the blood volume and the blood does not give up fluid to form urine The condition is somewhat similar to that produced by *excessive vomiting from intestinal obstruction This must be an* important factor in causing oliguria and azotemia Meyler produced azotemia in guinea pigs by repeated bleeding the blood urea rising as high as 200 to 300 mg per cent Administration of sufficient amounts of water prevented the azotemia

(c) *Absorption of Blood From the Intestinal Tract* —Borst attributed azotemia to the rapid absorption of urea formed from the blood in the intestinal tract, and this interpretation has been adopted by others However Johnson gave 1200 to 1500 cc of blood to four different patients by stomach tube during a period of six to eight hours The blood urea rose only moderately and transiently except in one patient whose urea clearance was only 50 per cent of normal in which instance it rose to 54 mg per cent The absorption of blood would help to explain the azotemia but not the oliguria

(d) *Increased Destruction of Body Proteins* —Meyler concluded that there is an increased destruction of body proteins

It seems highly probable that the chief cause of azotemia after gastrointestinal hemorrhage is the dehydrating effect of the loss of blood Low blood pressure is an important contributory influence in those who develop shock

Campbell and Stickney published the report of a patient who recovered from a hemorrhage resulting from duodenal ulcer, after the blood urea had risen to 652 and creatinine to 24 mg per cent

3 **Azotemia from Low Blood Pressure** (27 cases) —There are 27 cases in which the azotemia was probably due in large measure to a very low blood pressure All of the patients were in severe shock for a few days prior to death The shock was caused by fractures in 6 cases and by severe abdominal injuries in 3 Other causes of shock were coronary thrombosis perforated ulcer and carcinoma of the colon or stomach The systolic pressures ranged from 60 to 90 mm

was moderate to severe hydropic degeneration of the tubules in the other 18 cases the tubules were normal

4 **Postoperative Azotemia** (16 cases) —This is not a well-defined group from the point of view of causation since more than one factor is usually concerned Frequently there is a period of low blood pressure and there may be vomiting It is sometimes difficult to keep the patient well hydrated A terminal bronchopneumonia may be a contributory factor In 7 of our 16 cases there was hydropic de-

cases) —In 11 cases the

There

from

e de

cases) —In occasional in

e blood urea is markedly

increased (See page 44) and in a few cases of encephalomalacia and cerebral hemorrhage there is a high blood urea when the blood pressure is normal and the patient well hydrated. In our 7 cases the renal tubules were normal.

7. **Azotemia in Pneumonia.**—In 13 cases of pneumonia with azotemia there was hydropic degeneration of the proximal tubules in 6.

8. **Azotemia from Burns.**—Severe burns may cause oliguria and azotemia. The blood plasma escapes into the burned area causing hemoconcentration. The mechanism of the oliguria is like that of dehydration.

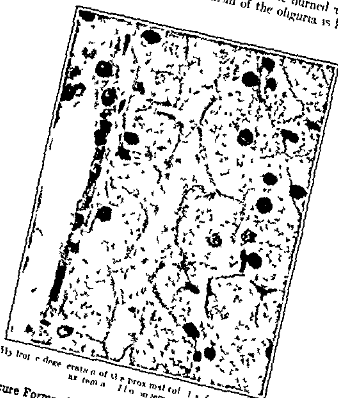


Fig. 60. Hydropic degeneration of the proximal tubules from a case of extrarenal azotemia. Photomicrograph.

9. **Obscure Forms of Azotemia.**—In 42 of our cases no satisfactory cause of the azotemia was found. Some were associated with severe infections. In 4 cases of this miscellaneous group there was hydropic degeneration of the proximal tubules.

Hydropic degeneration of the proximal tubules was found in about 22 per cent of the 112 cases of extrarenal azotemia (Fig. 60). This suggests strongly that injury of the proximal tubules is an important element in extrarenal azotemia.

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CHAPTER IX

EXUDATIVE INTERSTITIAL NEPHRITIS (PYELONEPHRITIS)*

INFLAMMATIONS of the interstitial tissues of the kidneys are commonly called pyelonephritis since in the majority of instances both the pelvis and the renal parenchyma are involved But pyelonephritis is not always an accurate descriptive term since cortical abscesses occur not infrequently without involvement of the pelvis and a mild pyelitis may exist without notable extension into the parenchyma these conditions may be designated cortical abscesses and pyelitis respectively

One objection to the use of the term 'interstitial nephritis is that this name was formerly applied to the contracted kidneys of chronic glomerulonephritis and primary hypertension because of the secondary condensation of connective tissue about the atrophic tubules But the older terminology has been in disuse so long that there will probably be no confusion from the use of this accurately descriptive term

The most important feature of this group of renal diseases is that they are caused by the lodgment of bacteria in the kidneys Glomerulonephritis and some of the tubular diseases are caused by toxic substances of bacterial origin but in exudative interstitial nephritis the bacterial bodies lodge in the kidneys and provoke an inflammatory reaction The causative organisms may be recovered from the kidney by cultural methods

A CORTICAL ABSCESS

Cortical abscesses of [illegible] then be appropriately called [illegible] types of cortical suppuration [illegible] le small abscesses carbuncle and perinephric abscess

(a) **Multiple Small Abscesses** — These are chiefly of anatomical interest since they are usually found in autopsy material in association with staphylococcic bacteriemia and there may have been no direct clinical evidence of their presence In persons dead of staphylococcic bacteriemia it is not uncommon to find multiple cortical abscesses which have not yet extended to the pelvis The abscesses vary from microscopic dimensions to a diameter of 1 cm or more, and are usually visible on the surface of the kidney after the capsule has been removed (Fig 67) In sections of such kid-

* Pages 293 to 319 are quoted with some alterations and additions from an article published in Surgery (Bell E T., Surgery 11 261 1942)

neys it may often be determined that the abscesses begin in glomeruli and then extend into the adjacent tubular areas The bacteria evidently lodge in the glomerular capillaries where they are attacked by polymorphonuclear leukocytes In the early stages numerous leukocytes pass through the glomerular capillaries and are carried through the tubules toward the pelvis The tubules associated with infected glomeruli are filled with polymorphonuclear leukocytes Bacteria are carried in this way through the tubules to the renal pelvis This is the reason we so often see streaks of suppura



FIG 67 Multiple abscesses of the kidney Photograph

tion extending radially from the cortex to the apex of the pyramid When the tubule becomes plugged with leukocytes the infection spreads beyond its lumen into the adjacent tissue

A microscopic section through a small abscess shows a central mass of cocci surrounded by a zone of necrosis beyond which is a dense wide zone of polymorphonuclear leukocytes The central necrosis is caused by the necrotizing toxin liberated by the staphylococci In abscesses of subacute or chronic course the polymorphonuclear cells may be replaced partly or entirely by macrophages or lymphocytes

As stated above multiple small abscesses are found most frequently in cases of frank staphylococcic bacteriemia but they are also frequent in those dead of diabetic coma and are seen occasionally in other diseases in which there was no clinical evidence of renal disease Apparently these abscesses are caused by E coli and staphylococci and the infection evidently reaches the kidney through the blood stream

Although no direct evidence is available it is highly probable that small abscesses may heal leaving as residues only small scars or lymphocytic infiltrations

(b) **Renal Carbuncle** —Carbuncle refers to a large multilocular honeycombed abscess Good descriptions have been given by Brady O Conor and Patch The lesion is much more often unilateral than bilateral The patient exhibits symptoms of a septic infection with localizing signs in the region of the involved kidney but there is commonly no pyuria

Usually an obvious source is demonstrable—a carbuncle furuncle or cellulitis of the skin A few cases follow sore throat Staphylococci are found in the carbuncle The infection may break through the renal capsule to form a perinephric abscess

Brady who collected 9[illegible] cases from the literature recommends drainage rather than nephrectomy

(c) **Perinephric Abscess** —This refers to suppuration about the kidney outside of its capsule It is widely believed that perinephric abscesses always represent an extension of a cortical abscess through the renal capsule but Vermooten maintains that they may develop outside the renal capsule and are not extensions of a cortical suppuration The etiology is the same as that of cortical abscess Surgical drainage is usually recommended especially when the kidney is not extensively destroyed

B PYELONEPHRITIS

The majority of infected kidneys show involvement of both the pelvis and the parenchyma and may be appropriately designated as pyelonephritis Pyelonephritis occurs both with and without obstruction of the urinary tract If simple renal abscesses without pyelitis be excluded the obstructive type is about twelve times as frequent as the non-obstructive but attracts less attention since the renal symptoms are overshadowed by the major illness responsible for the obstruction

In our [illegible] autopsies there were 1838 cases of hydronephrosis of varying degrees of intensity About 60 per cent of these showed gross infection of the kidneys When the obstruction was in the ureters above the bladder such as occurs from ureteral stricture and external compression of the ureters the incidence of infection in the kidneys was 25 to 40 per cent But when the obstruction was below

the bladder as in hypertrophy or carcinoma of the prostate and urethral stricture the incidence of infection was 70 to 80 per cent

The Route of Infection *Ascending Infections* —As noted above obstructive lesions of the urethra bladder and prostate produce infection of the kidneys about twice as frequently as obstruction of the ureters *above the bladder* Obstructions which distend the bladder are usually associated with cystitis the ureteral orifices tend to become dilated and there is *opportunity for reflux of infected urine* into the ureters These facts suggest that ascending infection plays an important role in the development of pyelonephritis resulting from obstruction of the lower urinary tract On the other hand when the block is in the ureter above the bladder it is difficult to understand how ascending infection can occur

Experimentally pyelonephritis may be produced in rabbits by introducing infection into the bladder and then obstructing the urethra in dogs it may be produced without obstruction by infecting the bladder and cutting the ureteral orifices so that they remain open (Gruber and Rabinovitch)

In low urinary tract infections in man the ureters and the bladder form a common chamber as the result of dilatation of the ureteral orifices Upon contraction of the bladder infected urine is forced into the ureters and the bacteria may be transported to the pelvis of the kidney by mechanical dissemination through the urine by to and fro movements or by the motility of the organisms *e g* colon bacilli

When the infection reaches the renal pelvis it produces pyelitis and in the earlier stages a direct extension of the inflammation into the medullary pyramids may be seen The infection may spread directly from the mucosa into the renal parenchyma or it *may reach the parenchyma through minute tears of* the mucosa which result from pelvic distention In retrograde pyelograms it is sometimes noted that the radiopaque substance escapes into the peripelvic tissues (pyelo-interstitial or pyelovenous reflux) and it is believed that this mechanism comes into play in obstructive hydronephrosis In animals substances injected up the ureter under pressure pass directly into the veins (pyelovenous reflux) and the veins of the kidney may be readily injected through the ureter

Hematogenous Infections Pyelonephritis developing in the absence of urinary obstruction is generally believed to be of hematogenous origin In the case of ureteral obstructions the infection is also presumably hematogenous since none of the factors which favor ascending infection are present It is possible that the infection reaches the kidney through the blood stream in some cases with low urinary obstruction It is known that a positive blood culture may frequently be obtained after operations on the lower urinary tract and even after catheterization (Scott Young) The urethral chill is attributed to bacteremia

It is well established that hydronephrosis predisposes the kidney to hematogenous infection If the ureter of one kidney of a rabbit be ligatured and staphylococci be injected intravenously forty-eight hours later, it will usually be found that multiple abscesses develop in the obstructed kidney but not in its normal mate It is therefore easily possible that bacteria from the infected bladder enter the blood stream and thus reach the cortex of the hydronephrotic kidneys

In the absence of obstruction it is assumed that the infection is of hematogenous origin, but in the presence of hydronephrosis ascending and hematogenous infections cannot be distinguished with certainty

Lymphogenous Infections — A few writers have supported the view that infection spreads from the bladder to the kidney through the periureteral lymphatics (Eisendrath Sweet) The chief evidence in support of this hypothesis is the presence of a lymphocytic exudate in the outer wall of the ureter This finding is however more readily explained as a chronic ureteritis similar to a chronic pyelitis

Bacteriology — Nearly all writers agree that colon bacilli are responsible for the great majority of infections of the urinary tract

[illegible]

know the proportions of colon and staphylococcic infections in the two groups However, it is clear that in the non-obstructive group which comprises about 8 per cent of the pyelonephritides the staphylococci are chiefly responsible since the infection usually originates in a known staphylococcic lesion such as a furuncle or carbuncle (Nesbit) Discrete cortical abscesses are due to staphylococci but diffuse inflammations are more often caused by colon bacilli Frequently a colon bacillus infection is superimposed on a staphylococcic inflammation

(a) **The Obstructive Type** —In pyelonephritis associated with obstruction the clinical picture is usually dominated by the disease responsible for the hydronephrosis such as hypertrophy of the prostate carcinoma of the bladder and carcinoma of the uterus but evidences of infection (fever leukocytosis pain or tenderness in the region of the kidneys etc) may be superimposed on those of the major illness

The age and sex distribution of the obstructive type of pyelonephritis correspond to that of hydronephrosis (Fig 23) During the third fourth fifth and sixth decades it predominates in females because of pregnancy and carcinoma of the uterus but after that time there is a great preponderance in males chiefly because of prostatic disease

The pyelonephritis of pregnancy exhibits special features Hydro-

von Illyes found 145 on the right 48 on the left and 39 bilateral Only a few patients gave a history of pyelitis in childhood The chief symptoms are chills fever leukocytosis renal pain and pyuria By means of drainage and chemotherapy most of the patients may be cured before the onset of labor but about 15 to 20 percent of the cases result in abortion or premature delivery The maternal mortality is about 3 per cent

Pyelonephritis during the puerperal period is somewhat less frequent than during pregnancy and generally develops during the first week Pyelonephritis occasionally recurs during a subsequent pregnancy but there is no satisfactory evidence that it causes toxemia Rarely the pyelonephritis of pregnancy continues as a chronic pyelonephritis but we have no example of this in our collection

In the paralytic and congenital types of hydronephrosis the associated pyelonephritis is easily recognized clinically In all forms of hydronephrosis infection destroys more or less of the renal parenchyma and hastens the onset of uremia

(*b*) **The Non obstructive Type** —This form may be called hematogenous or descending pyelonephritis and it is what clinicians usually have in mind when they speak of pyelonephritis As pointed out above however the obstructive type is twelve times as frequent as the non obstructive in autopsy material There is usually no difficulty in distinguishing the two types at autopsy but in chronic non-obstructive cases the shrinkage of the cortex may produce some enlargement of the pelvis and an associated inflammation of the ureter may cause a partial mechanical or paralytic obstruction

1 *Acute Hematogenous Pyelonephritis* —This lesion blends with cortical abscesses to such an extent that no sharp separation is possible We have grouped under this heading only the cases in which cortical abscesses were associated with gross involvement of the renal pelvis and have classified all cases of less than four months duration as acute There are a large number of cases of cortical abscesses in our autopsies but there are only 60 good examples of acute pyelonephritis

The chief symptoms are fever renal pain and tenderness dysuria tenesmus pyuria leukocytosis and anemia Weiss and Parker found the disease relatively common in early childhood during pregnancy and in old age In children malformations in the urinary tract are a contributory cause and in older subjects dia

betes is often a predisposing influence The prognosis is usually favorable

Referring to the 60 fatal cases found in our autopsy records it is noteworthy that there was in most instances an associated disease usually of infectious nature which was largely responsible for death and over hadowed to some extent the symptoms referable to the kidneys For convenience our 60 cases will be divided into four groups with respect to age

Children Under One Year of Age —There are 7 cases in this group 3 males and 4 females the ages being one month two months two months three months four months seven months and nine months respectively Two patients had otitis media and meningitis 1 had mastoiditis 1 had pharyngitis and 1 had an initial upper respiratory infection In the 2 remaining cases there was no disease other than the pyelonephritis The duration varied from ten to thirty days The blood pressures were not recorded At autopsy in each case both kidneys showed cortical abscesses with extensions into the pelves

Children from One to Ten Years Old —There were 5 cases in this

ci es were an upper respiratory infection acute osteomyelitis meningococcic meningitis and acute enterocolitis respectively In the fifth case there was a moderate unilateral hydronephrosis of undetermined cause which may have been the initial site of the infection The blood pressures were not recorded At autopsy the kidneys showed bilateral abscesses and suppurative pyelitis

There is an extensive literature on acute pyelonephritis in children Prior to 1909 it was generally regarded as a pyelitis on the assumption that the renal parenchyma was not involved In 1909 Thomson and McDonald reported 25 cases 21 girls and 4 boys with 21 recoveries In two autopsies on boys aged four months and seven months they found cortical suppuration as well as pyelitis In 1910 Thiemich reported 7 autopsies in 6 of which there was infection in the renal parenchyma

Wieland in 1918 described 45 cases with 4 deaths There were 35 girls and 10 boys In nurs ng nfants the sexes are al ...

organism found Twelve of the 21 cases had infection outside the kidneys The disease was bilateral in 12 instances on the right in 7 and on the left in 2 cases

It is now generally agreed that the pyelitis of children is

The pyelonephritis of pregnancy exhibits special features Hydro-

von Illyes *found 145 on the right 48 on the left* and 39 bilateral Only a few patients gave a history of pyelitis in childhood The chief symptoms are chills fever leukocytosis renal pain and pyuria By means of drainage and chemotherapy most of the patients may be cured before the onset of labor but about 15 to 20 percent of the cases result in abortion or premature delivery The maternal mortality is about 3 per cent

Pyelonephritis during the puerperal period is somewhat less frequent than during pregnancy and generally develops during the first week Pyelonephritis occasionally recurs during a subsequent pregnancy but there is no satisfactory evidence that it causes toxemia Rarely the pyelonephritis of pregnancy continues as a chronic pyelonephritis but we have no example of this in our collection

In the paralytic and congenital types of hydronephrosis the associated pyelonephritis is easily recognized clinically In all forms of hydronephrosis infection destroys more or less of the

may be called
what clinicians
onephritis As

pointed out above however the obstructive type is twelve times as frequent as the non-obstructive in autopsy material There is usually no difficulty in distinguishing the two types at autopsy but in chronic non obstructive cases the shrinkage of the cortex may produce some enlargement of the pelvis and an associated inflammation of the ureter may cause a partial mechanical or paralytic obstruction

1 *Acute Hematogenous Pyelonephritis* —This lesion blends with cortical abscesses to such an extent that no sharp separation is possible We have grouped under this heading only the cases in
gross involvement of
than four months
of cases of cortical

*abscesses in our autop*sies but there are only 0 good examples of acute pyelonephritis

ter
fo
pre
urinary *tract are a contributory* ...

betes is often a predisposing influence The prognosis is usually favorable

Referring to the 60 fatal cases found in our autopsy records it is noteworthy that there was in most instances an associated disease, usually of infectious nature which was largely responsible for death and overshadowed to some extent the symptoms referable to the kidneys For convenience our 60 cases will be divided into four groups with respect to age

Children Under One Year of Age —There are 7 cases in this group, 3 males and 4 females the ages being one month, two months two months, three months, four months, seven months and nine months respectively Two patients had otitis media and meningitis, 1 had mastoiditis, 1 had pharyngitis and 1 had an initial upper respiratory infection In the 2 remaining cases there was no disease other than the pyelonephritis The duration varied from ten to thirty days The blood pressures were not recorded At autopsy in each case both kidneys showed cortical abscesses with extensions into the pelves

Children from One to Ten Years Old —There were 5 cases in this group 3 females and 2 males, the ages being 18 months two years, three years six years and eight years respectively The duration varied from one to three weeks The complicating infections in 4 cases were an upper respiratory infection, acute osteomyelitis meningococcic meningitis and acute enterocolitis respectively In the fifth case there was a moderate unilateral hydronephrosis of undetermined cause which may have been the initial site of the infection The blood pressures were not recorded At autopsy the kidneys showed bilateral abscesses and suppurative pyelitis

There is an extensive literature on acute pyelonephritis in children Prior to 1909 it was generally regarded as a pyelitis on the assumption that the renal parenchyma was not involved In 1909 Thomson and McDonald reported 25 cases 21 girls and 4 boys with 21 recoveries In two autopsies on boys, aged four months and seven months, they found cortical suppuration as well as pyelitis In 1910 Thiemich reported 7 autopsies in 6 of which there was infection in the renal parenchyma

Wieland in 1918 described 45 cases with 4 deaths There were 35 girls and 10 boys In nursing infants the sexes were about equal [illegible]

in 6 and on the left in 2 cases

It is now generally agreed that the pyelitis of children is

pyelonephritis In most instances it is secondary either to some obvious focus of infection elsewhere or to a respiratory or intestinal infection The majority of the patients recover but a few die and a few develop chronic pyelonephritis Chronicity is favored by an anomaly which prevents drainage of the kidneys With modern methods of treatment the percentage of recoveries should be notably increased and the duration of the illness shortened

Wharton Gray and Guild made a careful study of 30 girls and young women from three to fourteen years after acute pyelitis in childhood One had severe chronic pyelonephritis and 16 others had slight but definite abnormalities in the urinary tract but no symptoms One had a recurrence of pyelitis during pregnancy and another went through pregnancy without difficulty

Persons from Ten to Forty Years of Age —There are 12 cases in this group 10 females and 2 males the ages being seventeen nineteen twenty-two twenty three twenty four twenty-six twenty seven twenty nine twenty nine thirty two thirty four and thirty four years respectively The duration varied from two weeks to two months The predisposing cause in 4 patients was diabetes one of whom was a boy aged seventeen years In 1 patient the renal infection followed a peritonsillar abscess and in another it was the outcome of puerperal endometritis In one instance the disease followed an upper respiratory infection Monocytic leukemia was the cause of one death in this group Apart from the 4 cases of diabetes and the 1 of monocytic leukemia death was apparently due to uremia and this was established by the high blood urea nitrogen in 2 instances (urea nitrogen 101 173 mg per cent) In 2 cases one kidney *was removed shortly before death but the infection continued in the* other kidney and uremia developed The disease was bilateral in each of the 12 cases

[illegible] 8 of the 12 cases In six patients

In

for

microscopic study In another the pressure ranged from 100 14 to 150/90 and no renal arteriolosclerosis was found

Persons Over Forty Years of Age —There are 36 cases in this group 17 males and 19 females Thirty were bilateral and 6 unilateral The causes of death in the bilateral group were as follows *Uremia 14 cases diabetes 6 cases and one each of the following* pyemia pneumonia carcinoma of rectum carcinoma of tongue pernicious anemia prostatic abscess suppurative arthritis cirrhosis of the liver primary hypertension and chronic glomerulonephritis The duration of renal symptoms varied from two weeks to three and one half months The involvement of the kidneys was usually severe but in only 14 cases was renal insufficiency the major cause of death

The blood pressures were recorded in 18 of the 36 cases In 7 of

the medulla to the pelvis Usually the purulent areas have a patchy distribution and are separated by areas of normal parenchyma, but in cases of extreme severity very little healthy parenchyma can be found

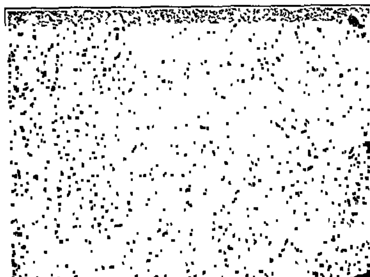


Fig 68 —Acute hematogenous pyelonephritis There is a purulent interstitial exudate which has destroyed most of the tubules Photomicrograph

Microscopic sections through the affected areas show the tubules largely replaced by cellular exudate (Fig 68) In the acute stage the exudate is composed of polymorphonuclear and large mononuclear leukocytes The tubules in the infiltrated areas are largely destroyed, and when a patient with a lesion of this type survives for several months the cortex atrophies, *producing deep pits on the surface of the kidney*

Acute Interstitial Nephritis —Acute interstitial nephritis is described as a separate entity but it is closely related to the interstitial lesions just described The chief distinction from acute

pyelonephritis In most instances it is secondary either to some obvious focus of infection elsewhere or to a respiratory or intestinal infection The majority of the patients recover but a few die and a few develop chronic pyelonephritis Chronicity is favored by an anomaly which prevents drainage of the kidneys With modern methods of treatment the percentage of recoveries should be notably increased and the duration of the illness shortened

Wharton Gray and Guild made a careful study of 30 girls and young women from three to fourteen years after acute pyelitis in childhood One had severe chronic pyelonephritis and 16 others had slight but definite abnormalities in the urinary tract but no symptoms One had a recurrence of pyelitis during pregnancy and another went through pregnancy without difficulty

Persons from Ten to Forty Years of Age —There are 12 cases in this group 10 females and 2 males the ages being seventeen nineteen twenty two twenty three twenty four twenty six twenty seven twenty nine twenty nine thirty two thirty four and thirty-four years respectively The duration varied from two weeks to two months The predisposing cause in 4 patients was diabetes one of whom was a boy aged seventeen years In 1 patient the renal infection followed a peritonsillar abscess and in another it was the outcome of puerperal endometritis In one instance the disease followed an upper respiratory infection Monocytic leukemia was the cause of one death in this group Apart from the 4 cases of diabetes and the 1 of monocytic leukemia death was apparently due to uremia and this was established by the high blood urea nitrogen in 2 instances (urea nitrogen
was removed shortly
other kidney and ur
each of the 12 cases

Blood pressures were recorded in 8 of the 12 cases In six patients the systolic pressure was not above 130 mm Hg at any time In one the pressure was 148/96 but no kidney tissue was available for microscopic study In another the pressure ranged from 100/64 to 150/90 and no renal arteriolosclerosis was found

Persons Over Forty Years of Age —There are 36 cases in this group 17 males and 19 females Thirty were bilateral and 6 unilateral The causes of death in the bilateral group were as follows Uremia 14 cases diabetes 6 cases and one each of the following pyemia pneumonia carcinoma of rectum carcinoma of tongue pernicious anemia prostatic abscess suppurative arthritis cirrhosis of the liver primary hypertension and chronic glomerulonephritis The duration of renal symptoms varied from two weeks to three and one half months The involvement of the kidneys was usually severe but in only 14 cases was renal insufficiency the major cause of death

The blood pressures were recorded in 18 of the 36 cases In 7 of

the 18 cases the systolic pressure was 150 mm. or higher, the lowest pressure being 150/100 and the highest 220/120. Six of the 7 cases [illegible]

[illegible]

patients with acute pyelonephritis [illegible]

[illegible]

the medulla to the pelvis. Usually the purulent areas have a patchy distribution and are separated by areas of normal parenchyma, but in cases of extreme severity very little healthy parenchyma can be found.

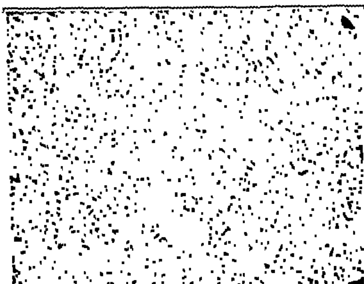


Fig. 68. Acute hematogenous pyelonephritis. There is a purulent interstitial exudate which has destroyed most of the tubules. Photomicrograph.

Microscopic sections through the affected areas show the tubules largely replaced by cellular exudate (Fig. 68). In the acute stage the exudate is composed of polymorphonuclear and large mononuclear leukocytes. The tubules in the infiltrated areas are largely destroyed, and when a patient with a lesion of this type survives for several months the cortex atrophies, producing deep pits on the surface of the kidney.

Acute Interstitial Nephritis. Acute interstitial nephritis is described as a separate entity, but it is closely related to the interstitial lesions just described. The chief distinction from acute

diffuse hematogenous pyelonephritis is the character of the cellular exudate and the relationship to acute infectious diseases notably to scarlet fever Typical cases such as those first described by Councilman are quite rare and occur chiefly during scarlet fever *about one week after the development of the rash* *In the fatal* cases there is severe oliguria or anuria and uremia Blood urea and creatinine are greatly increased and the blood pressure may be elevated The kidneys are swollen to about twice their normal size and on microscopic examination there is found a massive



Fig 69 Acute interstitial nephritis following scarlet fever The interstitial exudate composed chiefly of mononuclear cells Photomicrograph

diffuse infiltration of the interstitial tissues with plasma cells and mononuclear leukocytes (Fig 69) When there is only a moderate patchy infiltration the patient recovers and such cases may be recognized years later by the presence of cortical depressions under which are patches of lymphocytic infiltration

There are only three examples of acute interstitial nephritis in our autopsy records The following case is typical

A male, aged eighteen years, was admitted to the hospital nine days

[illegible]

tion (Fig [illegible])



Fig 70 Chronic bilateral hematogenous pyelonephritis No 13 Table 41 Weight of each kidney 40 gm Note the finely granular surface Photograph

Rarely there are similar but less extensive plasma cell infiltrations in the kidneys after diphtheria puerperal sepsis and other infections There are no sharp distinctions from ordinary interstitial inflammations, even after scarlet fever the exudate may consist partly or largely of polymorphonuclear leukocytes

2 *Chronic Hematogenous Pyelonephritis* —Infections of more than four months duration may be classified as chronic In this discussion only the non-obstructive type is considered The symptoms vary with the severity of the disease Frequently there are acute exacerbations at irregular intervals during which the symp-

toms are more pronounced During exacerbations there is commonly fever leukocytosis renal tenderness or pain nausea pyuria etc *In the intervals between* acute attacks and in chronic forms of low intensity there may be only a low grade fever a loss of appetite or fatigability Pyuria is found only during exacerbations

The disease may persist for many years before death is brought about by uremia or infection

In the literature chronic pyelonephritis is applied almost exclusively to contracted kidneys but a marked shrinkage of the *kidneys is not a necessary feature When death results from an* acute exacerbation of a chronic infection the kidneys may be of increased size (No 9 Table 41)

Both Staemmler and Pfeiffer found pyelonephritic contracted kidneys very common in autopsy material and estimated that from one-fourth to one third of contracted kidneys were of this type From one third to one-half of their cases were unilateral But *these estimates must include types of disease which we have classi*fied as hydronephrosis and unilateral dwarfed kidneys In our 59 064 autopsies there are only 22 cases of chronic bilateral pyelonephritis of the non obstructive type and only 13 of these were typical bilateral contracted kidneys The disease is more common in females than in males

The macroscopic changes in the kidneys are characteristic and have been well described by Staemmler and Pfeiffer The external surfaces show coarse sunken areas separated by islands of persistent cortex The sunken areas are regions of marked cortical atrophy and the elevated areas are portions of intact cortex Sometimes the process is so diffuse that the external surfaces appear *finely* granular (Fig 70) The extent of the atrophy is of course greater in unilateral than in bilateral disease The thin cortices of the kidneys may give an impression of hydronephrosis although there is little or no enlargement of the pelves

Microscopically the shrunken cortical areas show a marked atrophy of the tubules with an infiltration of small lymphocytes and an increase of fibrous tissue When the original infiltration *is in* the medulla on [illegible] trophy from destruction of [illegible] infiltrated *areas usually* [illegible] t of parenchyma persisting in the chronic stage naturally depends upon the extent of the original inflammatory exudate In some instances there is a heavy infiltration of lymphocytes throughout the parenchyma (Fig 71)

In bilateral forms of pyelonephritis death occurs before atrophy has reached the extreme degree that is found in unilateral cases *The atrophic cortical areas are interspersed* with normal tubules and glomeruli The completely atrophied segments are composed

almost entirely of hyaline glomeruli, atrophic tubules and areas of lymphocytic infiltration

In unilateral disease the atrophy may become extreme, and

[illegible]

The arteries supplying the atrophic segments of the kidneys



FIG 71 Chronic pyelonephritis showing masses of lymphocytes between the tubules Photomicrograph

show thickened walls and this appearance has been mistaken for primary arterial disease But this alteration in the arteries is a disuse atrophy and it may usually be distinguished from arteriosclerosis without difficulty The distinctive feature is that the arteries in disuse atrophy show severe medial fibrosis but no intimal disease In the larger arteries the shrinkage in size is manifested by extreme folding of the internal elastic lamina (Fig 73) In the smaller arteries (Fig 74) there is no intimal disease but there is extreme medial fibrosis, practically all the smooth muscle having been replaced by collagen The sclerotic arteries of atrophic

pyelonephritis are therefore the effect of the disease and not its cause as maintained by Weiss and Parker.

The Blood Pressure in Bilateral Chronic Pyelonephritis.—Several writers have noted that bilateral pyelonephritis is occasionally accompanied by hypertension Haslinger, 1928, found no noteworthy increase of blood pressure, but Staemmler as well as Pfeiffer



Fig 72 —Severe unilateral atrophic pyelonephritis The entire thickness of the cortex is shown Note hyaline glomeruli lymphocytic infiltration atrophic segments of tubules filled with casts and the thick walled atrophic arteries Photomicrograph

found the pressure elevated not infrequently. Weiss and Parker found hypertension in about 50 per cent of their patients, but these investigators have confused their records by the inclusion of several obvious cases of malignant hypertension

Longcope, who is often quoted on this topic, stated that the blood pressure is seldom elevated during the early stages of the disease, but that hypertension was present in 10 of 15 advanced cases But of his 10 cases with hypertension 5 had renal arteriolosclerosis and 1 had chronic glomerulonephritis

Crabtree was not impressed with the frequency of hypertension

s disease

chronic bilateral pyelonephritis (Table 41) Hypertension was present in 8 cases, but 2 of these (Nos 3 and 6) had also chronic glomerulonephritis and another had severe renal arteriolosclerosis (No 7)



FIG 71 Diffuse atrophy of arteries in chronic atrophic unilateral pyelonephritis Note extreme folding of the internal elastic lamina and the absence of intimal thickening Elastic tissue stain Photomicrograph

In case No 14 there was a terminal acute thromboarteritis which was pres[illegible]
blood pre[illegible]
the heart[illegible]
tients h[illegible] tion of blood pressure such as occurs in primary hypertension the only instances of moderate cardiac hypertrophy were those with an associated chronic glomerulonephritis (Nos 3 and 6)

It may therefore be said that hypertension seldom occurs in uncomplicated chronic bilateral pyelonephritis, and that a severe

prolonged hypertension with cardiac hypertrophy in this disease is usually due to a complicating lesion such as chronic glomerulonephritis or renal arteriolosclerosis

An illustrative example of chronic bilateral pyelonephritis with contracted kidneys is as follows



FIG 74 —Small arteries from atrophic pyelonephritis Higher magnification of arteries shown in Figure 72 Severe medial fibrosis but no intimal disease Photomicrograph

No 13 Table 41 A ... was first seen on March 26 1940 fourteen years previousl

faces and

TABLE 41 —BILATERAL CHRONIC PYELONEPHRITIS WITHOUT URINARY OBSTRUCTION

No	Autopsy No	Age yrs	Sex	Duration	Blood urea nitrogen mg per cent	Blood pressure	Weight of heart gm	Weight of kidneys gm	Hyaline arterioles or other disease
1	34 2178	8	F	6 yr +	208	125/90	110	Very small	
2	25 304	20	M	2 yr	236	100/55	307	R 70 L 60	
3	39 2543	25	M	13 yr 10 mo	200	152/94	4?	R 75 L 43	Chr glomerulonephritis
4	37 3186	27	F	7 mo	2?0	130/90	300	R 100	?
5	39 1371	30	F	20 mo	NPN 28?	112/74 140/80	32?	R 74 L 100	0
6	41 ?017	34	M	6 mo	63	2?0/138	400	R 73 L 10	Chr glomerulonephritis
7	36 144?	44	F	28 yr 6 yr	199	198/140	2?0	L 100	3
8	26 615	4?	M	2 yr +	86	2 152/88 ?	280	290	0
9	25 464	4?	F	3 yr	48		250	R 590 L 100	0
10	30 1016	46	F	1 yr		160/8?	260	640	0
11	44 698	46	M	34 yr +	210	116/80	350	R 90 L 80	0
12	40-1753	48	1	28 yr	68	140/90 3 yr 110/80	?90	R 100	?
13	40 38?1	48	F	14 yr	NPN 80	2 da 115/65	190	R 40 L 40	0
14	36-1278	49	F	10 mo	5?	195/100	295	R 290 L 150	Acute thromboarteritis
15	28 164?	48	M	9 yr	145		350	R 60 L 1?0	0
16	19 224	59	M	2 yr 8 mo	PSP 3?	115/70	19?	300	0
17	40-?88	41	F	6	?0	104/74	2?	1??	
18	48 133		F	2	High	? 0	3	32	0
19	48 ?0	6?	F		NPN 72	98 4	340	3??	
20	47 1?32	68	F	+		120/?0	345	4	(
21	47 20?0	71	F	3 mo +	170	210/110 11?/?0	32	185	0
22	43 13	72	F	10 yr	10	1?0/88	24	16?	0

Microscopic sections show small areas of persistent parenchyma separated by large atrophic segments In the atrophic areas there is severe tubular atrophy with a lymphocytic infiltration and some increase of interstitial fibrous tissue

A case illustrating a complication with chronic glomerulonephritis follows

No 3 Table 41 A male aged twenty five years known to have had albuminuria at the age of twelve years and nocturia for many years He had had poor health for the past eighteen months and definite renal disease was recognized fourteen months before death Upon admission eleven days prior to his death he was drowsy and had a uremic odor on his breath The blood pressure was 157 88 and 152 94 Hemoglobin 58 per cent erythrocytes 2 500 000 leukocytes 10 800 Albumin ++ specific gravity of urine 1012 During a ten-day period with an average fluid intake of 2320 cc the average amount of urine daily was 946 cc Blood urea nitrogen 200 mg per cent creatinine 21 7 mg per cent

At autopsy there was a slight dependent edema The heart weighed 425 gm and showed left ventricular hypertrophy and moderate coronary atherosclerosis The right kidney weighed 75 gm and the left 43 gm The pelves and right ureter were dilated but the left ureter was of normal

size There was no obstruction in the urinary tract The cortices of both kidneys were markedly atrophic and the external surfaces were covered with coarse depressions

Microscopically the kidneys show a heavy lymphocytic infiltration especially in the medullary por
persistent normal glomeruli an
tubules are very atrophic and
hyaline glomeruli show evidence of a [illegible] proliferative glomerul[illegible]
but the *greater part of the atrophy is attributable to the heavy lymphocytic infiltration* The arteries and arterioles show no changes except a moderate disuse atrophy

The interpretation is a chronic pyelonephritis associated with chronic glomerulonephritis

Unilateral Pyelonephritis —In our autopsy records there are 145 cases of unilateral dwarfed kidney but aside from 18 cases of true hypoplasia and 16 examples of unilateral polycystic disease it is usually impossible to determine the cause of the atrophy with certainty In a few cases there is a lymphocytic exudate suggesting pyelonephritis but in the vast majority there is no evidence of
[illegible] of the hypoplasia
thick walled
much larger
In some instances it appears that hydronephrosis was responsible for the atrophy and in other cases atherosclerosis of the large arteries is suggested

None of the 145 cases was a surgical kidney in the sense that it was producing local symptoms In the great majority the atrophy was so extreme that little or no functioning parenchyma remained (Fig 10)

Recently the chief interest in unilateral pyelonephritis has centered about its supposed relation to hypertension Many cases have b
returned to
it was only
[illegible] rologists believe that any type
may produce high blood
ie view that all cases of

in hypertension with
[illegible]latt s experiments on
[illegible] of one renal artery
usually causes moderate hypertension The hypertension produced in this way is however not severe and does not persist permanently as it does when both renal arteries are constricted It is believed that the ischemic kidney secretes renin which causes *elevation of* blood pressure A very important feature of this experiment frequently overlooked is the fact that if the constriction of the artery is severe enough to produce atrophy *of the kidney* the blood

pressure will return to normal after the atrophy is well advanced In the experiment which Pedersen and I performed on obstruction of one renal vein the blood pressure began to decrease after two months and it was found that the obstructed kidney was markedly atrophic In two dogs with bilateral constriction of the renal arteries which I have studied the blood pressure was high for over eighteen months but then fell to normal levels and remained so for about one year before the animals were killed At



Fig 7a —Kidney of a dog about thirty months after application of a Goldblatt clamp to the renal artery Note disappearance of tubules Explanation in text Photomicrograph

autopsy in each case one kidney had developed a collateral circulation and was normal while the other showed extreme atrophy (Fig 7a) The only persistent parenchyma is an occasional atrophic tubule containing a cast These atrophic kidneys in the dogs were evidently incapable of producing renin and it may therefore be argued that human atrophic kidneys with minimum amounts of parenchyma are likewise incapable of producing renin There is no feature of the Goldblatt experiment which justifies the removal of a completely atrophic human kidney

The earlier literature concerning the effect of nephrectomy on hypertension is summarized in Table 42. Sixty-one cases are recorded in the table in which a diseased kidney was removed in the hope that a fall of blood pressure would result. Nos 2, 13, 16 and 37 cannot be considered cured since the duration of the postoperative period of normal blood pressure was not given. Similarly Nos 5, 6, 14 and 31 must be omitted from consideration since the period of observation was too short. It is well known that non specific operations such as hysterectomy often cause hypertension to subside for several months. The former practice of extracting teeth as treatment for hypertension was based upon the observation that a temporary fall of blood pressure frequently resulted. When the blood pressure remains at normal levels for as long as six months a palliative effect may be claimed but one should not speak of a cure unless the patient has been followed for at least one year since the blood pressure may return to its original high level after several months (Nos 11, 12). It must be determined that the patient has a persistent hypertension and not merely a labile blood pressure. In No 18 the evidence of hypertension is hardly satisfactory and in No 19 the marked variation in the preoperative blood pressure throws doubt upon the result.

TABLE 42.—EFFECT OF NEPHRECTOMY ON HYPERTENSION WITH UNILATERAL RENAL DISEASE

No	Author	Date	Age	Sex	Preoperative blood pressure	Postoperative blood pressure	Interval	Lesion
1	Boyd and Lewis	1938	31	M	180 100 200 120	124 84	6 5 mo	Large infarct
2	Leadbetter and Burkland	1938	5	M	170 110 145 85	Normal	?	Ectopic kidney muscle plug in artery
3	Nesbit and Ratliff	1940	37	M	180/110	Normal	1 yr	Pyelonephritis
4	Nesbit and Ratliff	1940	35	M	200 110	140 80	10 5 mo	Small contracted
5	Nesbit and Ratliff	1940	58	M	205 110	150 110	2 wk	?
6	Nesbit and Ratliff	1940	47	F	190 1[illegible]0	120 95	13 da	Pyelonephritis hydronephrosis
7	Nesbit and Ratliff	1940	28	F	220 110 280 140	220/110	3 mo	Pyelonephritis arteriosclerosis
8	Nesbit and Ratliff	1940	40	F	[illegible]00/1[illegible]0	200/125	?	25 gm arteriosclerotic
9	Nesbit and Ratliff	1940	24	M	170 100	130 64	5 mo	Hydronephrosis
10	Barney and Suby	1939	10	F	185 130	98/60	21 mo	Pyelonephritis
11	Crabtree	1938	14	M	250 170	130 ? high	1 wk 1 yr	Hydronephrosis
12	Crabtree	1938	27	F	180 ? 210 ?	120 76 145/90 196 124	3 wk 6 yr 11 yr	Pyelonephritis glomerulonephritis
13	Crabtree	1938	40	M	160 120 130 ?	Low	?	?
14	Ratliff	1939	51	F	180 100	1[illegible]0/80	At discharge	Tuberculosis
15	Ratliff	1939	32	M	230/170	155 110	?	Arteriosclerosis
16	Quinby	1923	14	M	250 170	138/90	?	Hydronephrosis
17	McIntyre	1939	34	M	180 104	134/78	10 mo	Pyelonephritis
18	Bothe	1939	7	F	130 85	110 [illegible]5	4 5 yr	Pyelonephritis
19	Butler	1937	7	M	12[illegible] [illegible]0 168 110	115/75	20 mo	Pyelonephritis
20	Butler	1937	10	F	190 120	9[illegible]/70	3 mo	Pyelonephritis
21	Barker and Walters	1940	42	M	170 1[illegible]0 200 140	130 90	2 yr	Pyelonephritis
22	Barker and Walters	1940	46	M	170 110	115 85	6 mo	Pyelonephritis
23	Barker and Walters	1940	34	[illegible]	180 115	12[illegible] 9[illegible]	1 yr	Pyelonephritis
24	Barker and Walters	1940	52	F	186 110	125 85	1 yr	Pyelonephritis
25	Barker and Walters	1940	7	F	[illegible]05 150	110 77	3 mo	Pyelonephritis
26	Patch	1940	12	F	160 115	106 68	5 mo	Pyelonephritis

TABLE 42 — EFFECT OF NEPHRECTOMY ON HYPERTENSION WITH UNILATERAL RENAL DISEASE — (Continued)

No	Author	Date	Age	Sex	Preoperative blood pressure	Postoperative blood pressure	Interval	Lesion
27	Everett	1940	?6	F	152/108	Same	7 mo	?
28	Everett	1940	8	F	160 115	120 70	8 mo	?
29	Everett	1940	37	F	190/130 (maximum)	150 115	6 mo	?
30	Everett	1940	41	F	170 110	135 95	7 mo	?
31	Everett	1940	36	F	160 100	120 80	? mo	?
3	White et al	1943	39	M	170 100	Normal	8 mo	Hydronephrosis calcu
33	Chute et al	1939	51		180 100	1 0 80	6 mo	Tuberculosis
34	Chute et al	1939	3		220 130	155 110	9 mo	Rupture of kidney
35	Chute et al	1939	37		180 110	1?0 90	4 mo	Abnormality of kidney
36	Morton	1939	34		180 ?	12 84	1 yr	Hydronephrosis
37	Richards	1941	37		210 150	118 78	?	Tuberculosis
38	Howard	1940	5	F	158/90 ?00 140	1 0 70	5 mo	Aneurysm of renal artery sympathectomy also
39	Abeshouse	1941	52	M	200 110	152 108	3 yr	Pyelonephritis
40	Abeshouse	1941	50	M	??0 116	260 140	4 mo	Pyelonephritis
41	Abeshouse	1941	36	F	160 90	140 90	yr	Tuberculosis
42	Abeshouse	1941	21	F	48 86	1 0 80	4 yr	Tuberculosis
43	Abeshouse	1941	24	M	144/92	120 78	1 yr	Tuberculosis
44	Abeshouse	1941	48	F	210/110	158/9?	13 mo	Pyelonephritis with calculus
4	Abeshouse	1941	49	M	166 84	13 80	3 yr	Pyelonephritis with calculus
46	Abeshouse	1941	52	M	19 110	140 108	13 mo	Pyelonephritis with calculus
47	Abeshouse	1941	38	F	160 100	146/100	2 mo	Pyelonephritis with calculus
48	Abeshouse	1941	51	F	2 0 120	230 126	4 mo	?
49	Abeshouse	1941	8 5	M	140 94 160 100	120 82	7 yr	Hydronephrosis
50	Abeshouse	1941	56	M	180 120	170 10	4 yr	Pyonephrosis
51	Abeshouse	1941	61	M	184 110	142 90	2 yr	Pyonephrosis
52	Schroeder and Fish	1940	3	M	210 130	No change	?	Calculus with hydronephrosis
53	Schroeder and Fish	1940	30	F	60 150	200 110	3 wk	Weight 12 gm pyelonephritis ?
54	Schroeder and Fish	1940	30	F	270 150	120 80 18 110	?	?
55	Schroeder and Fish	1940	26	F	19 /130	180 114	16 mo	Weight 25 gm
56	Schroeder and Fish	1940	33	M	19 138	150 100 130 90	16 mo	Pyelonephritis weight 60 gm clinical improvement
57	Schroeder and Fish	1940	19	F	220 140	172 142 96 80	3 mo	Hypoplasia clinical improvement
58	Oppenheimer	1939		M	200 130	140 100	16 mo	Pyelonephritis
59	Kennedy Barker and Walters	1944	7	F	170 110 225 178	106 70	5 yr	Atrophic pyelonephritis
60	Semans	1944	2 5	M	200 134	98 62	3 yr	Atrophic pyelonephritis
61	Sweeney and Pace	1943	21	F	210 120	Low	1 yr	Pyelonephritis

In the group which were followed from six months to one year there were 13 cases in which the blood pressure returned to normal levels 2 cases in which there was no decrease and 3 cases in which the pressure was reduced but still above normal

In the group followed for over one year there are 8 cases (Nos 10 21 42 45 49 51 59 and 60) in which the blood pressure returned to normal but Nos 42 45 and 49 are examples of only moderate hypertension In 5 cases followed for over one year the blood pressure was at a lower level but the patient still had hypertension and in 4 patients the blood pressure was unaffected

In Crabtree s cases (Nos 11 and 12) the blood pressure showed a postoperative fall but subsequently returned to a high level Three cases have come under my personal observation Two females

aged fourteen and twenty six years and a male nine years old Each had severe hypertension of long duration and one low functioning small kidney that was producing no renal symptoms In the 2 females the small kidneys showed chronic pyelonephritis and arteriolosclerosis in the male there was only arterio and arteriolosclerosis The kidneys contained only minimal amounts of functioning parenchyma Nephrectomy had no favorable effect on the hypertension in these 3 cases there was not even a temporary decrease

Since the cases shown in Table 42 were collected a number of other reports have been published An extensive experience with nephrectomy in hypertensive subjects was reported by Ratliff and associates in 1947 Their report deals with 49 nephrectomies in 2055 hypertensive individuals Seventeen of the 49 patients who underwent nephrectomy [illegible]
were obtained in 7
ritis in 4 of 11 with
and in 4 of 13 with [illegible] ephrosis The follow up period was over one year in all but 8 cases

Crosbie and Fischman obtained spectacular temporary improvement by removing a small non functioning kidney but the patient died of uremia ten months later

Maitland reported a case of severe hypertension with retinitis in a woman 20 years of age A poorly functioning kidney showing chronic pyelonephritis was removed The symptoms disappeared immediately and the patient was well one year later

Oster reported a case of unilateral hydronephrosis in a boy seven years of age due to an aberrant renal artery Four months after ligature of the artery the blood pressure which previously had been

(Tables 1 to 5) Forty of the 81 (49 per cent) had hypertension Of the 64 persons over fifty years of age 61 per cent had hypertension This is somewhat higher than in Wetherby s dispensary patients and it suggests a causal connection between unilateral dwarfed kidney and hypertension But is is highly probable that hypertension with its associated vascular disease is responsible for the dwarfed kidney i e that the dwarfed kidney is an effect and not a cause of hypertension The few cases in which material from the large kidney was available showed hyaline arteriolosclerosis

Interesting data on the relation of unilateral renal disease to hypertension was furnished by Pearman Thompson and Allen These investigators found the incidence of hypertension in 500 cases of each of the following diseases as follows Pyelonephritis 9 per cent nephrolithiasis 7 per cent duodenal ulcer 4 per cent adenomatous goiter without hyperthyroidism 10 per cent disease of the gallbladder 7 per cent In 2000 cases of hypertension the

incidence of gallbladder disease was 4 4 per cent adenomatous goiter 2 5 per cent duodenal ulcer 1 3 per cent and arthritis 6 3 percent These data suggest that pyelonephritis like adenomatous goiter and arthritis is merely associated with hypertension and is not a causative factor

In Table 42 it may be seen that almost every type of unilateral renal disease except neoplasm has been suggested as a cause of hypertension The only feature common to these various lesions is atrophy of the parenchyma Howard attributed hypertension to an aneurysm of the renal artery (No 38) but his patient had an extensive sympathectomy as well as nephrectomy If it be true that any form of unilateral renal disease may cause hypertension a study of a group of patients subjected to unilateral nephrectomy should be informative

Crabtree and Chaset 1940 reported a study of 150 nephrectomized patients The preoperative blood pressure averaged somewhat lower than Wetherby s control data Fourteen of the 150 had a blood pressure above 150/100 mm Hg Twelve of these were followed subsequently and it was found that 3 had a slightly lower blood pressure but the others showed no change or an increase Elevation of blood pressure was not the rule even in chronic bilateral pyelonephritis

Friedman and associates 1942 surveyed 193 patients who had had nephrectomy for unilateral renal disease There was no relation between the type of renal disease and the level of the blood pressure Seven per cent of those with hypertension showed a significant decline postoperatively but 22 per cent developed hypertension in the postoperative period In the others the blood pressure was unchanged

Friedman and associates 1942 studied the renal function of 5 patients before and after nephrectomy for unilateral renal disease Three patients showed a significant decrease of blood pressure but none showed a complete return to normal despite the fact that there was no ischemia of the remaining kidney as measured by the diodrast clearance

A significant study was reported by Weiss and Chasis in 1943 of a patient who had hypertension with unilateral atrophic pyelonephritis The diseased kidney weighed 33 gm Nephrectomy had no effect on the blood pressure After nephrectomy it was shown that the remaining kidney had a normal function and was not ischemic yet the hypertension persisted

Langley analyzed 103 cases subjected to nephrectomy He regarded 47 of these as successful He believes that nephrectomy is most apt to be successful in young patients with no family history of hypertension and with a non functioning kidney on one side and a normal kidney on the other Retinitis is not a contraindication The duration of the hypertension is not a deciding factor

It appears that unilateral renal disease is seldom the cause of

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our 133 cases there were 35 with a fairly early lesion usually restricted to one kidney In 6 of these the tuberculous nodule 1 to 3 cm in diameter *was restricted to the cortex and did not extend*

the cortex Cortical lesions that do not reach the pelvis would probably not produce symptoms but they suggest that some medullary (clinical) lesions represent extensions from the cortex In 24 cases the lesions *were restricted to the medulla and adjacent pelvic mucosa It appears therefore that clinical tuberculosis may begin* in the cortex and extend into the pyramid but that a majority begin in the pyramid Wildbolz believes that all clinical tuberculosis begins in the pyramids No satisfactory explanation of this phenomenon has been offered It has been suggested that tubercle bacilli escape through minute lesions in the glomerular capillaries and are then carried with the *glomerular filtrate to the collecting tubules* They *may of course reach the medulla directly without* going through a glomerulus

Clinical Features —There may be attacks of renal colic from passage of blood clots through the ureter Pain in the kidney may be due to the inflammation or to hydronephrosis from ureteral obstruction Frequency of urination is due chiefly to tuberculosis

ulcers and deformities of the pelvis can usually be seen except in

bercles may be seen in the

he sediment is sufficient to establish the diagnosis but the presence of an occasional acid fast bacillus without pyuria is insufficient evidence since the organism

may

Harr ilts with bone and joint tuberculosis although *there were usually no symptoms referable to the kidneys When tubercle bacilli are found in* ureteral urine there are always tuberculous lesions in the kidneys but the lesions may be minimal and this finding alone does not justify nephrectomy (Thomas and Kinsella)

Bilateral Lesions The usual experience of urologists is that

50 per cent are bilateral—67 of our 133 cases. The higher incidence of bilateral disease in autopsies is to be expected since these are more advanced cases. It appears that over 80 per cent of the cases are unilateral at first. In our series 57 per cent of the secondary type, i.e., those associated with pulmonary tuberculosis and 40 per cent of the primary type were bilateral.

Pathology.—A majority of investigators describe the earliest lesion as tuberculosis of one or more renal papillae with ulceration of the surface (Fig. 77). Numerous polymorphonuclear leukocytes are present in the central necrotic area and tubercle bacilli are abundant. The cortex is not involved at first.



Fig. 77.—Ulcerative tuberculosis of the kidney. Note caseous necrotic tissue replacing the pyramid. Photograph.

In our series of 133 cases 24 were early medullary lesions of this type. However, there were 5 cases of cortico-medullary type in which the lesion extended from the tip of the papilla to the mid cortical region. Since abscesses always progress from cortex to medulla it appears probable that these began as cortical lesions and then extended into the medulla but possibly they represent extensions in the opposite direction. There were 6 cases with one to three cortical tuberculous abscesses from 1 to 3 cm. in diameter.

which had not extended into the medulla There is no good reason for regarding these cortical lesions as enlarged miliary tubercles and it seems justifiable to conclude that some cases of chronic tuberculosis begin in the cortex

After the papillary ulceration has been established the disease spreads over the entire pelvic mucosa and down into the ureter The ureter may become obstructed by tuberculous tissue causing a hydro-pyonephrosis The distended pelvis is filled with caseous purulent material and its walls are formed by tuberculous tissue The cortex undergoes atrophy because of the obstruction and it is gradually destroyed by the progressive tuberculous inflammation This type is called tuberculous pyonephrosis After the kidney has been destroyed a pyonephrosis may remain stationary for a long time and it may even shrink to become a fibrous sac filled with inspissated caseous material There are 13 examples of atrophic pyonephrosis in our autopsies Active tuberculous tissue can always be found there is never complete healing but the process becomes relatively latent Some calcification is frequently observed

In another anatomical type the ureter is not obstructed and the tuberculous inflammation spreads through the cortex causing enlargement of the kidneys There were 15 examples of this type in our autopsies

Renal tuberculosis sometimes terminates in generalized miliary tuberculosis In our series there are 19 cases of generalized miliary tuberculosis which developed from the renal lesion Braasch found associated tuberculosis of the genital tract in 73 per cent of the males

Healing Medlar offered evidence that minimal tuberculous *lesions may heal and be converted into fibrous tissue* *Baggenstoss* and Greene presented satisfactory anatomical evidence that isolated miliary tubercles in the renal cortex may heal completely Patients with minimal clinical lesions may become symptom free and resume their former occupations (Thomas and Kinsella

group

renal

o for

several years (Wildbolz Reid) Randall reported an unusual case in which a patient with bilateral renal tuberculosis was still living and in fair condition thirty seven years after the onset of the disease Some of the cases of unilateral tuberculosis in which clinical recovery occurs are instances in which the affected kidney is completely destroyed and walled off This process has been called autonephrectomy Anatomically it is an atrophic pyonephritis

No instance has been reported in which advanced clinical tuberculosis healed without destruction of the kidney and even these closed atrophic kidneys do not show complete histological healing

The chance of clinical recovery of an advanced lesion is rather small and nephrectomy appears to be the best treatment for all unilateral lesions except those with minimum involvement of the kidney. Statistics indicate that 50 to 60 per cent of unilateral cases are permanently cured by nephrectomy.

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2 **Syphilis of the Kidneys** —Gumma of the kidney was reported occasionally in the older literature but is now evidently very rare. In some of the old reports it appears that the author was dealing with a neoplasm or Hodgkin's disease rather than a gumma.

Small interstitial foci of lymphocytes may be found in the kidneys in both congenital and acquired syphilis. In 13 of 200 cases of acquired syphilis Rich found spherical nodules of lymphocytes. These lesions are not associated with clinical symptoms of renal disease.

Syphilitic Nephrosis Munk laid great stress upon syphilis as a cause of lipoid nephrosis but a majority of subsequent investigators agree that syphilis plays an insignificant role in this disease. However Herrmann and Marr maintain that syphilis may produce a clinical syndrome closely resembling that of lipoid nephrosis. The argument presented by these investigators is that the patient has syphilis and that his renal symptoms improve or disappear under antisyphilitic therapy. There have been no satisfactory pathological studies on cases of this type.

In one of our cases of chronic glomerulonephritis there was severe edema and the Wassermann reaction was strongly positive. Antisyphilitic therapy had no effect and the kidneys at post mortem were not different from other cases of chronic glomerulo-

nephritis I have the impression that syphilitic nephritis is merely some form of nephritis in a patient who also has syphilis

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syphilis)



FIG 78 —Acute disseminated lupus erythematosus Note necrosis of capillary walls *There is also a moderate degree of endothelial proliferation Photomicrograph*

3 **Disseminated Lupus Erythematosus** —The generalized form of lupus erythematosus is characterized by a cutaneous eruption most conspicuous on the face where it has a butterfly distribution and extending to the trunk and extremities It is a febrile disease in which ... are frequent A majority of the patients a... results fatally Slight to moder... but *occasionally the*

urine is normal throughout the illness A few patients die of uremia but the majority have no renal insufficiency

Baehr Klemperer and Schifrin 1935 found a coarse verrucous endocarditis in 13 of 23 cases but in a later paper 1941, they found endocarditis in only 6 of 20 cases Stickney and Keith found endocarditis in 3 of 15 cases In our 27 cases there were 3 instances of bacterial endocarditis and one of the rheumatic type There were two instances of old rheumatic mitral valvulitis Baehr Klemperer and Schifrin 1935 described patchy thickenings

patchy thickenings in only 5 of 15 cases These lesions were found in 12 of our 27 cases but they were pronounced in only 6 instances (Table 44) The lesion is
with necrosis of the capilla
of some toxic substance
in acute glomerulonephritis

Other types of glomerular lesions were also found in our cases (Table 44) In 7 instances there was moderate diffuse endothelial proliferation (grades 1 and 2) and in 2 cases (Nos 1 and 3) there was

TABLE 44 LUPUS ERYTHEMATOSUS THE NUMERALS REFER TO THE INTENSITY OF THE PROCESS

	Autopsy No	Age	Sex	Durat on of symptoms	Endocard t s	Diffuse pro fera ve glomerul t s	Focal g omerulitis	Patchy thicken ng of cap ary walls	Blood p essu e
1	32 910	11	F	3 mo	+	3	0	0	
2	32-551	2	F	4 mo	0	0	3	0	25/85
3	24 807	20	F	6 mo	+	3	0	2	135 88
4	33 1975	33	F	1 yr	0	2	0	3	110 62
5	33 1964	25	M	17 da	0	0	0	0	
6	41 542	52	F	mo	0	2	0	2	160 100
7	37 500	38	F	1 wk	0	0	0	1 –	98 50
8	36-1126	20	F	2 yr	+	1	0	1	
9	25-944	22	F	4 5 mo	0	0	0	0	110/70
10	40 2494	46	F	3 mo	0	1	0	1	108 60
11	29 1071	55	F		0	0	0	3	110 60
12	39-445	31	F	3 yr	0	1	0	1	115 65
13	39-1607	16	M	? wk	0	0	0	0	106 4
14	26 772	27	F	16 mo	0	1	0	0	
15	40 532	4	F	1 yr	0	0	0	0	
16	40 966	58	M	6 mo	0	0	0	0	130 78
17	41 542	52	F	? mo	0	1	0	3	160/100
18	41 1317	20	F	2 mo	0	0	0	0	110 70*
19	42 56	29	F	2 mo	0	0	0	0	132/78
20	43 1254	35	F	3 mo	0	0	0	1 –	104 60†
21	43 2157	16	F	4 mo	0	0	0	2	116 68‡
22	41 83	51	F	10 da	Il	0	)	0	130 75
23	45 80	47	M	1 y	+	0	0	0	—
24	43 778	18	F	1 wk	0	0	0	0	
25	46 243	33	F	10 r	0	0	0	0	115/85
26	46-2127	29	F	8 mo	old		2	1	170 110
27	48 878	20	F	2 yr	0	0	0	0	120 58

* F rst attack 2 yrs p ev ously
† Suppurat ve per card t s
‡ Strep vir dans septicemia

a clinical acute glomerulonephritis with uremia In No 11 there was a diffuse thickening of all the capillary basement membranes such as occurs in lipoid nephrosis, and the thick membranes were colored blue with Mallory-Heidenhain In No 2 there was a widespread focal glomerulonephritis of the embolic type in the absence of endocarditis In No 26 there was a severe acute gomerulitis in-
[illegible], with extensive thrombosis

[illegible] types of glomerular lesions *may be found in a series of cases of lupus erythematosus* The most frequent form is a patchy thickening of the capillary walls When this lesion is conspicuous it is strong evidence for lupus erythematosus, but its absence does not exclude this disease

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LEUKEMIA OF THE KIDNEYS

Leukemia is more related to neoplasms than to inflammations,
[illegible]

[illegible]
great reduction of renal parenchyma

CHAPTER IX

DISEASES OF THE BLOOD VESSELS

A PASSIVE CONGESTION

at r there is

ately severe album u
sponsible for the mild injury of the glomeru u ue
distended capillaries sometimes rupture and allow erythrocytes to escape into the urine There is little or no increase of blood urea
l he f enolsulphonephthalein output may fall as low as 30 per
c

there
are
(43)
causes net o ion
may
om
bosis o and
cause uremia The following is a n of
The patient a male aged forty three ars
on July 23
weeks later
The

diagnosis of throm o
October 12 and again on November 20
showed no excretion by either kidney There was heavy albuminuria and the specific gravity of the urine fell to 1015 The blood urea nitrogen reached 100 mg per cent early in December but was 54 mg six days before death The blood pressures were as follows August 9 120 85 August 23 125/90 September 14 152 90 September 28 174 112 October 17 174/112 November 12 120 90 and December 15 126 70 mm Hg Death December 21 At autopsy the kidneys each weighed about 200 grams There was a thrombosis of the inferior vena cava which extended somewhat
al veins The right renal vein was
closed

through
ou and the
temporary hypertension are passive
congestion This is convincing evidence that venous obstruction

of the kidneys may produce hypertension and it is in agreement with the experiment which Pedersen and I made in 1930 (page 381)

B INFARCTION

Infarction of the kidneys is usually due to embolism the emboli being detached thrombi from the heart valves in bacterial endocarditis The clinical evidences of infarction are pain in the region of the kidney and hematuria The infarcts with bacterial endocarditis are never sufficiently extensive to produce uremia



FIG 9 Severe cortical atrophy produced by chronic obstruction of the renal vein This patient developed hypertension See text page 3 9 Photomicrograph

Multiple small infarcts occur in generalized thromboarteritis and especially in periarteritis nodosa (page 331) Numerous small infarcts may produce uremia

In rare cases of eclampsia extensive bilateral cortical necrosis occurs which may be due to extensive thrombosis of the small renal arteries

C PERIARTERITIS NODOSA

[illegible]

widespread and variable distribution of the vascular lesions the clinical picture is correspondingly complex and difficult to interpret Among the more frequent manifestations are fever leuko [illegible]

[illegible]

sist of perivascular accumulations of leukocytes but some of them are small aneurysms There is inflammation in the adventitia and media which often extends into the intima to produce stenosis or thrombosis or the inflammation may weaken the intima and produce an aneurysm Occasionally no gross nodular thickenings are present and the diagnosis must be made microscopically

Periarteritis nodosa is discussed under renal diseases since renal [illegible]

[illegible]

uremia was due in 4 instances to massive occlusion of the small arteries and in one to thrombosis of the large renal arteries In 3 cases uremia was caused by a severe diffuse exudative and prolifera- [illegible]

[illegible]

sure was recorded

D SENILE ARTERIOSCLEROTIC KIDNEYS

In old age the kidneys usually show adherent capsules and a few coarse pits on their external surfaces Sometimes the pits are large and numerous but the amount of atrophy is seldom sufficient to cause a f [illegible]

[illegible]

of primary hypertension It is important for the pathologist to know that kidneys with adherent capsules and coarsely pitted surfaces rarely represent clinical renal disease

E PRIMARY (ESSENTIAL) HYPERTENSION

In the discussion of hypertension it is important to distinguish the secondary from the primary type When the elevation of blood

pressure is caused by a known disease or experimental procedure it is called secondary Primary hypertension includes the type or types in which the etiology has not been established

Primary hypertension may be defined as an elevated blood pressure usually permanent of unknown etiology It is not a sharply circumscribed entity since the boundary between normal and abnormal blood pressure is not well defined and there are varying degrees of hypertension In defining hypertension some allowance must also be made for the age of the individual

The Normal Blood Pressure —*It* is very difficult to decide upon the upper limit of normal blood pressure and there are differences of opinion among investigators on this point It is generally agreed however that a blood pressure of 150/90 mm Hg at any age is abnormal Some observers believe that pressures above *140 90 mm Hg are too high at any age It is also generally believed* that pressures above 140/90 in persons under thirty years of age are abnormal and that pressures above 130/80 in children are too high The above accepted opinions are based upon numerous observations that persons with pressures above the indicated levels have *a higher morbidity and mortality from hypertensive* disease than those with lower pressures

The average blood pressure of a population cannot be accepted as the normal since hypertensive individuals are included in such studies Augustin approached the problem in a somewhat different way in that he recorded the systolic blood pressures of 8805 individuals over twenty-one years of age and arranged the pressures in quartiles in the different decades The upper quartile (25 per *cent of the group in each decade) were the ones with the highest* pressures and these were considered abnormally high The upper quartile in males was as follows twenty-one to forty years 130+ mm Hg forty one to fifty years 140+ fifty one to sixty years 155+ sixty-one to seventy years 160+ The upper quartile in *females was as follow twenty one to thirty years* 125+ thirty one to forty years 135+ forty one to fifty years 150+ fifty one to sixty years 170+ sixty one to seventy years 180+ The difficulty with this conception seems to be that in *the older age* groups more than 25 per cent of the population have hypertensive disease

Diehl and Hesdorfer followed 155 young men for five to ten years (average seven years) The average age at the first examination *was nineteen and four fifths years and* at the second examination twenty six and four fifths years No increase of average blood pressure was observed over this period—some were higher and others lower on the second examination

Hines and Lander determined the blood pressure in a group of individuals ten years after the first examination and found that hypertensive disease was four or five times as frequent in those

who had a high normal than in those who had a low blood pressure at the first examination This observation suggests that hypertensive disease often begins with a slight elevation of blood pressure many years before the pressure reaches a level which we regard as hypertensive disease

It is generally agreed that the normal systolic pressure at puberty is below 120 mm Hg Between the age of puberty and thirty years the majority of normal persons have a pressure below 120 70 mm Hg Those in this age group with pressures from 135 80 to 140 90 commonly have no symptoms but this group seems to furnish most of the cases of clinical hypertension found two or three decades later

There are racial differences in the frequency of hypertension Kean found a low incidence in Panamanians (chiefly mestizos) and an almost complete absence of hypertension among the Cuna Indians Hypertension was seven times as frequent in West Indian negroes as in native Panamanians

The Frequency of Hypertension —Numerous reports deal with the frequency of hypertension in different age groups and in general there is agreement An extensive study was made by Wetherby who recorded the blood pressures of 5540 dispensary patients—3258 women and 2282 men These were persons who had some complaint but they were taken from all the dispensary services and only a small percentage complained of hypertensive symptoms In the group forty to forty nine years old 12 3 per cent of the men and 40 8 per cent of the women had systolic pressures of 150 mm Hg or higher and 2 9 per cent of the men and 21 5 per cent of the women had pressures of 180 mm Hg or more In the group sixty to sixty nine years old 42 8 per cent of the men and 66 8 per cent of the women had systolic pressures above 150 mm Hg and 15 3 per cent of the men and 34 per cent of the women had pressures above 180 mm Hg In the group over fifty years of age hypertension in the sense of 150 90 mm Hg or higher was present in 38 per cent of the men and 57 5 per cent of the women

Master and associates recorded the blood pressures of 8483 males and 6366 females over forty years of age Hypertension in the sense of 150 90 mm Hg or higher was found in about one-fourth of the men and one third of the women in the fifth decade In the sixth decade about 40 per cent of the men and over 50 per cent of the women had hypertension About two-thirds of women over sixty years old and of men over seventy years old have hypertension If hypertension be defined as 140 90 mm Hg or higher about one-half of males and about 60 per cent of females over forty years of age have hypertension

Russek and associates determined the blood pressure of 5331 men forty to ninety five years of age They found that 69 1 per cent of those over sixty years of age had a systolic pressure of 140 mm Hg

or higher but only 41 9 per cent had a diastolic pressure above 90 mm Hg The systolic pressure increases with age but the average diastolic pressure shows little change after the sixth decade They believe that primary hypertension cannot be defined in terms of the systolic pressure alone

In elderly persons the systolic pressure is related to the decreased

lesions even though the diastolic pressure is not above 90 mm Hg The strain on the vascular system is an average of the systolic and diastolic pressures

Ayman found that patients with primary hypertension do not have a fixed diastolic pressure The systolic pressure fluctuates within a range of 20 to 40 mm Hg and the percentage variation in the diastolic pressure is as great as in the systolic

It is clear therefore that hypertension in the sense of an elevated blood pressure is much more frequent in older women than in older men and that nearly one-half of the population over fifty years of age has hypertension in some degree But the great majority have a moderate hypertension without symptoms From our autopsy records it appears that about 13 per cent of persons over fifty years of age die of some form of hypertensive disease but about three-fourths of individuals who have hypertension die

Criteria for the Diagr
study a systolic pressure
sons of all ages and 140
years of age is regarded as primary hypertension after all known causes of hypertension have been excluded A diastolic pressure of 95 mm Hg or higher is regarded as hypertension even if the systolic is not high The reason for the adoption of these figures as the upper limit of normal blood pressure is that pressure above these levels is attended with a definite increase of mortality from hypertensive disease

Difficulty is encountered in persons with labile blood pressure In such individuals variations of 30 to 40 mm Hg in the systolic pressure may be observed from time to time the higher readings occurring especially during emotional disturbances The lower pressure probably corresponds more closely to the usual level but there is some evidence that transitory hypertension of this type may pass over into permanent hypertension

In clinical hypertension of cardiac type a previously high blood

pressure sometimes falls to normal during cardiac decompensation or as a result of coronary thrombosis We have a number of records in which this phenomenon occurred It therefore follows that when a patient is first seen in the final attack of heart failure we

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to use left ventricular hypertrophy more than any other feature One must of course exclude all cases of primary right ventricular hypertrophy as well as all cases in which there is an assignable cause of left ventricular hypertrophy such as valvular defects and chronic glomerulonephritis

There are however difficulties in using heart weight alone as

diseases In the usual case of carcinoma of the stomach with marked emaciation the weight of the heart is often 100 gm less than that of well nourished individuals

One might expect the weight of the heart to correspond to the intensity and duration of the hypertension but this is often not the case There is a variation in the response of the individual heart in rare instances a systolic blood pressure of over 200 mm Hg and of many years duration is associated with a heart weighing no more than 300 gm On the basis of the heart weight alone

persons with

with clinical

symptoms of hypertensive disease It includes all cases of hypertensive renal insufficiency chronic myocardial failure without other assignable cause hemorrhage or softening of the brain on a vascular basis coronary sclerosis or thrombosis with hypertension or cardiac hypertrophy and a small group with hypertensive symptoms in which death was due to another disease The several clinical groups are subdivided with respect to blood pressure and cardiac hypertrophy so that these factors may be evaluated

Age Distribution —The distribution of all types of hypertension by decades is shown in Figure 80 The percentages are based upon 17 708 autopsies on individuals over ten years of age—11 826 males

and 5882 females In this graph are 1520 cases and all but 1(died of some form of hypertensive disease The graph shows th age at the time of death not the time of onset of the disease

It will be noted in the graph that only about 2 5 per cent of th deaths in the fourth decade are due to hypertensive disease bu after the fifth decade the incidence increases greatly reaching maximum of about 15 per cent in the seventh and eighth decade In persons over fifty years of age, hypertensive disease is the caus of death in about 13 per cent George Fahr calculated from vita

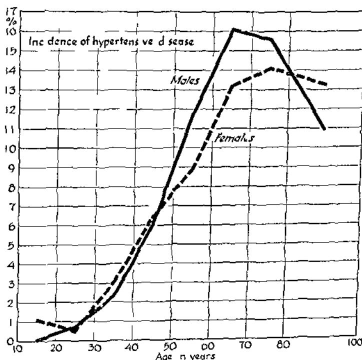


Fig 80 —Deaths f om hypertens ve d sease arranged accord ng to age and sex

statistics that about 23 per cent of all deaths in persons over fifty

hypertension is chiefly a disease of persons past middle life it may occur in children The youngest person in our series had onset of symptoms at the age of eight years Taussig and Remsen reported a case in a boy two years old

It is to be emphasized that about three-fourths of persons with hypertension die of another disease and that the majority with moderate hypertension have no symptoms.

Sex.—In the entire group over ten years of age 9.3 per cent of males and 6.9 per cent of females died of hypertensive disease. There is no significant sex difference in death ratios up to the age of fifty years but after this period the death ratio from hypertension is somewhat greater in males (males 14.1 per cent, females 11.9 per cent). If we examine the individual clinical groups it is noteworthy that myocardial insufficiency and apoplexy show about the same sex incidence but coronary disease is much more frequent

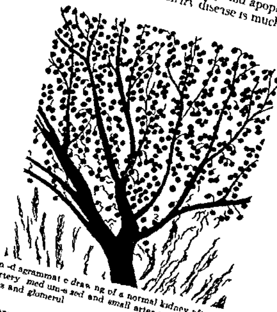


Fig. 81.—Semi-diagrammatic drawing of a normal kidney after arterial injection showing large artery, medium-sized and small arteries, pre-arterioles, afferent glomerular arterioles and glomeruli.

in males. Approximately the same percentage of deaths from renal insufficiency occurs in the two sexes but females preponderate before the age of fifty years and males after fifty years.

The Renal Arteries and Arterioles in Hypertension.—In this discussion of hypertension we are concerned mainly with the alterations in the kidneys. The vessel entering the renal arterial system is shown in Figure 81. The vessel entering the cortex between the pyramids is called a large artery and its subdivisions are called small arteries. The term arteriole is applied to the afferent glomerular vessel which supplies only one glomerulus. Prearteriole refers to the terminal small vessel from which most of the arterioles arise. It is very important to distinguish the arterioles and pre-arterioles

from the larger vessels since the changes in the latter are related much more to the age of the individual than to the level of the blood pressure

The Control Group —The controls are shown in Table 45 The e are ind
and no
hearts
in male
trols will now be described



FIG 82 —Section of a small artery showing no intimal thickening (Grade 0) Photomicrograph

(a) *The Small Arteries* In the control group i e individuals who had neither hypertension nor cardiac hypertrophy there is a progressive increase in the thickness of the intima with increasing
grade 1
in Fig
ly and
npletely
largely

of elastic tissue (Fig 85)

TABLE 45 —INCIDENCE AND DEGREE OF INTIMAL DISEASE IN THE SMALL ARTERIES OF THE CONTROL GROUP WITH RESPECT TO AGE

Age yrs	No of cases	Degree of involvement per cent			
		0	1	2	3
0–10	12	100.0	0	0	0
10–20	7	71.0	29.0	0	0
20–30	26	46.0	42.0	12.0	0
30–40	34	26.5	53.0	11.7	8.8
40–50	58	8.6	56.9	24.1	10.4
50–60	114	0	58.8	22.8	18.4
60–70	86	0	34.9	39.5	25.5
70–80	81	0	18.5	32.1	49.4
80+	31	0	12.9	45.1	42.0
Over 50	312	0	37.3	32.1	30.5

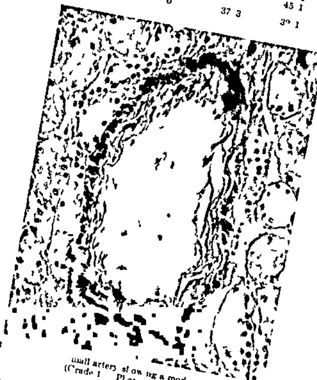


Fig 83 —Small artery showing a moderate intimal thickening (Grade 1 Photomicrograph

The increase in the frequency and the degree of intimal disease in the successive decades is shown in Table 45 The change first appears in the second decade and after the age of fifty years there are no entirely normal renal arteries

In Table 46 there is shown a comparison of the intensity of intimal disease in the small arteries of the control group over fifty years of age with that of hypertensive individuals It will be noted

that Grades 2 and 3 are found in 62 6 per cent of the controls and over 80 per cent of the hypertensives These data suggest that intimal disease in vessels of this caliber is an age change which develops independently but is somewhat accelerated by hypertension

TABLE 46 —INTIMAL THICKENING OF SMALL RENAL ARTERIES WITH HYPERTENSION

	No of cases	Degree of involvement per cent			
		0	1	2	3
Controls over 50 years	311	0	37 3	32 1	30 5
Myocardial (A_1)	226	0 9	12 8	32 3	54 0
Cerebral (B_1)	194	0	11 3	31 4	57 2
Coronary (C)	80	1 2	16 2	40 0	42 5

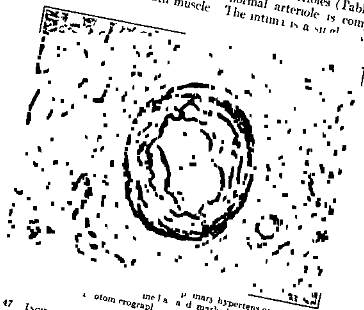


FIG 84 Section of a small artery showing a marked intimal thickening (Grade 3) The adjacent pre arteriole also shows severe intimal thickening *Photomicrograph*

(*b*) *The Pre arterioles* —The pre-arterioles are the small terminal arteries from which the majority of the afferent glomerular arteri-

The hyaline and the fibers are usually separable but frequently they blend to such an extent that the intima is best described as fibro-hyaline. The intimal thickening increases in frequency and intensity with increasing age. The percentage of individuals with normal pre-arterioles becomes progressively less with advancing age (Table 47), but even after the age of seventy years over one third of the subjects have normal vessels. In the table Grade I_p refers to the presence of small focal lesions while Grades 1 to 3 indicate a diffuse involvement. The pre-arterioles in the control group are affected much less frequently than the small arteries (Table 45) but somewhat more frequently than the afferent arterioles (Table 48).

The Arterioles.—The wall of a normal arteriole is composed almost entirely of smooth muscle. The intima is a single layer of



Fi[illegible] [illegible] otomicrograph [illegible] me[illegible] a[illegible] [illegible] primary hypertension. Elastic tissue stain [illegible] and marked intimal thickening due ch[illegible]

TABLE 47. INCIDENCE AND DEGREE OF INVOLVEMENT OF THE PRE-ARTERIOLES IN THE CONTROL GROUP

Age yrs	No. of cases	Degree of involvement per cent 0	I_p	1	2	3
0-10	12	100.0	0	0	0	0
10-20	7	100.0	0	0	0	0
20-30	[illegible]	[illegible]	3.8	3.8	0	0
30-40	34	79.4	17.6	3.0	0	0
40-50	58	67.2	15.5	13.8	1.7	1.7
50-60	114	64.0	20.1	14.0	1.8	0
60-70	86	57.0	20.9	19.8	0	2.1
70-80	81	35.8	35.8	21.0	7.4	0
80+	31	41.9	[illegible]	[illegible]	[illegible]	0
Over 50	312	52.6	25.0	17.9	3.2	0.7

TABLE 48.—INCIDENCE AND INTENSITY OF ARTERIOLAR DISEASE IN THE CONTROL GROUP WITH RESPECT TO AGE

Age, yrs	No. of cases	Degree of involvement, per cent				
		0	1p	1	2	3
0–10	12	100 0	0	0	0	0
10–20	7	100 0	0	0	0	0
20–30	26	88 5	7 7	3 8	0	0
30–40	34	79 4	17 6	0	0	3 0
40–50	58	72 4	17 2	8 6	0	1 7
50–60	114	71 0	18 4	8 8	1 8	0
60–70	86	62 8	22 1	11 6	3 5	0
70–80	81	50 6	28 4	17 3	2 4	1 2
80+	31	51 6	19 3	25 8	3 2	0
Over 50	312	61 5	22 1	13 4	2 6	0 3

endothelial cells. In the older individuals of the control group there is frequently a subendothelial deposit of a hyaline material. This is usually homogeneous but sometimes it exhibits a fibrillar structure and may appropriately be called fibrohyaline. The designation 1_p in Table 48 refers to occasional deposits of hyaline in the arterioles. Grades 1, 2 and 3 refer to a diffuse distribution of the alteration in the arterioles.

Relation of Arteriolar Disease to Age (Table 48).—It may be seen in Table 48 that the frequency and the intensity of arteriolar disease increase with age. All of the individuals of the control group were free of symptoms of hypertensive disease and had neither hypertension nor cardiac hypertrophy. In the group fifty to sixty years of age 29 per cent had abnormal arterioles and 10 6 per cent had definite arteriolosclerosis. In the group seventy to eighty years old 20 9 per cent had definite arteriolosclerosis. In the entire group over fifty years of age 16 3 per cent had arteriolosclerosis. Renal arteriolosclerosis is therefore an age change which develops independently of hypertension.

Relation of Arteriolosclerosis to Disease of the Small Arteries.—Arteriolosclerosis is never found except in association with a Grade 2 or 3 intimal thickening of the small arteries, but disease of the larger vessels is very common in the absence of arteriolar disease. One gets the impression that intimal disease of the larger vessels gradually extends into the arterioles.

In Table 49 the sex and age distribution of the control group over fifty years of age is shown. There is no difference in the incidence or severity of vascular renal lesions in males and females.

TABLE 49.—SEX AND AGE DISTRIBUTION OF THE CONTROL GROUP OVER 50 YEARS OF AGE

Age, yrs	Males	Females
50–60	77	37
60–70	60	26
70–80	60	21
80+	23	8
Total	220	92

Renal arteriolosclerosis, Grades 1 to 3, was found in approximately 16.3 per cent of each group.

The Relation Between the Level of the Systolic Blood Pressure and Arteriolosclerosis in the Control Group Over Fifty Years of Age.—In 208 cases with a systolic pressure from 90 to 129 mm. Hg the incidence of arteriolosclerosis, Grades 1 to 3, was 13.5 per cent; in 104 cases with a pressure of 130 to 139, 22.1 per cent. This suggests that there is some relation between the incidence of arteriolosclerosis and the level of the blood pressure even at pressures which lie within the normal range.

In Table 50 are shown 85 cases in which the systolic pressure ranged from 140 to 179 mm. Hg but in which the patient had no hypertensive symptoms. All of the persons in this group were over fifty years of age. It will be noted that the incidence of arteriolosclerosis is somewhat higher in this group than in those with pressures below 140 mm. Hg. Evidently arteriolosclerosis is more frequent in persons with very high blood pressure and hypertensive symptoms than in those with moderately elevated pressure and no symptoms.

TABLE 50. RELATION OF ARTERIOLOSCLEROSIS TO THE LEVEL OF THE SYSTOLIC BLOOD PRESSURE IN PERSONS OVER 50 YEARS OF AGE WITHOUT HYPERTENSIVE SYMPTOMS

Systolic blood pressure	No. of cases	Arteriolosclerosis Grades 1 to 3, per cent
Controls		
1. 90-129	208	13.5
2. 130-139	104	22.1
3. 140-149	19	25.8
4. 150-159	23	34.3
5. 160-169	21	42.9
6. 170-179	22	31.8
Total 3, 4, 5, 6	85	34.1

The Relation Between Arteriolosclerosis and the Size of the Heart in the Control Group Over Fifty Years of Age (Table 51).—It may be seen in Table 51 that arteriolosclerosis is definitely more frequent in association with hearts weighing above 300 gm. in males and 250 gm. in females than with hearts of smaller size.

TABLE 51. RELATION OF THE SIZE OF THE HEART TO ARTERIOLAR DISEASE IN THE CONTROL GROUP OVER 50 YEARS OF AGE

Weight of heart, g. Males	Females	Arteriolar disease, per cent: 0	1±	1	2	3	No. of cases
195-299	170-249	48.2	21.1	8.6	2.0	0	104
300-349	250-299	41.5	20.5	16.[illegible]	1.[illegible]	0	11[illegible]
350-400	300-350	3[illegible]	4.[illegible]	15	4.[illegible]	1.1	89

The Arteriolar Lesions in the Controls and in the Hypertensive Subjects.—The earliest lesion in an arteriole is a subintimal deposit

of a hyaline substance (Fig 86) This may take the form of small focal lesions here and there in the vessel This focal lesion is *referred to as 1_p in the tables The lesion then spreads and becomes* diffusely distributed in the arterioles, and the diffuse lesion is graded 1, 2 and 3 in the tables in accordance with its severity In Figure 86 two stages of the diffuse hyaline lesion are shown, the one on the left is Grade 1, the one on the right Grade 2 A diffuse Grade 1 lesion is shown under low magnification in Figure 87, and a



FIG 86 —Renal arteriolosclerosis There is a hyaline subintimal deposit Grade 1 in the arteriole on the left and Grade 2 in the arteriole on the right Photomicrograph

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hyalin in the proximal than in the distal portion of the arteriole The hyaline deposit is usually thicker in hypertension complicated by diabetes (Fig 88) Often one finds hyalin in the efferent arterioles, especially in *diabetics*

It is clear that renal arteriolosclerosis of moderate intensity is frequently found in persor

disease and whose blood

recognized normal limits

[illegible] In addition to those with

It appears that the most important factor in arteriolosclerosis



Fig. 87.—Primary hypertension without renal insufficiency. Grade 1 arteriolosclerosis. Note subintimal deposits of hyalin. Photomicrograph.

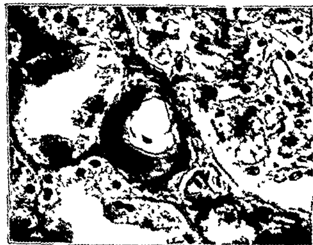


Fig. 88.—Cross-section of an afferent arteriole in a diabetic showing Grade 3 arteriolosclerosis.

in the control group is the age of the individual There can be no doubt that arteriolosclerosis may develop independently of hypertension since it is found frequently in association with a small heart and a low blood pressure, but there is a suggestion that it may influence the level of the blood pressure and the size of the heart since it occurs more frequently in the controls with larger hearts and higher blood pressures

It may be suggested that the older individuals are the ones with the larger hearts and higher pressures but a careful analysis shows that the size of the heart and the level of blood pressure in this group are not related to the age

Scriba also found many non hypertensives in the older age groups who had renal arteriolosclerosis Moritz and Oldt found renal arteriolosclerosis in non hypertensive subjects as follows thirty one to forty five years 7 per cent forty six to sixty years 9 per cent and sixty one years and over 16 per cent But these investigators used arteriole in the sense of an artery not over 100 microns in diameter which includes vessels which I have classified as *pre-arterioles and small arteries*

CLINICAL FORMS OF HYPERTENSIVE DISEASE

Group A The Myocardial Type

Because of the increased *peripheral resistance* the heart must contract more forcefully in order to supply an adequate amount of blood to the tissues The increased blood pressure is a measure of the increased work required of the heart The increased work of the left ventricle causes it to undergo hypertrophy since a larger stronger muscle is required to do the increased work But in spite of its increased size the left ventricle may become fatigued especially after exertion One of the frequent early signs of hypertensive disease is dyspnea on exertion due to temporary congestion of the lungs As the left heart failure progresses dyspnea becomes more pronounced and cyanosis may develop When *the right heart* begins to fail the patient develops edema and general venous congestion A slight degree of jaundice may appear as a result of *extreme passive congestion of the liver A systolic murmur* at the apex of the heart occurs frequently from relative mitral insufficiency due to dilatation of the left ventricle The blood pressure usually *remains high in the presence* of left heart failure but sometimes the

In the presence

t exclude hyper

before the onset

Over 50 per cent of the deaths from hypertensive disease are due to myocardial exhaustion With respect to the available data

the cases of the myocardial group may be arranged in 4 subgroups

Subgroup A_1 — This group comprises 226 cases In each instance the patient died of myocardial failure and the hearts weighed 350 gm or more in the females and 400 gm or more in males There was no known cau e of the cardiac hypertrophy other than increased blood pressure The systolic pressure was 150 mm Hg or higher in all but 7 cases which were included because the diastolic pressures ranged from 95 to 110 mm Hg The diastolic pressures were as follows 100 mm Hg or higher 175 cases 91 to 99 14 cases 81 to 90 20 cases 71 to 80 15 cases and below 75 mm Hg 2 cases There was a fairly close correspondence between the systolic and diastolic pressures most of the lower diastolic pressures occurring with systolic pressures below 160 mm Hg A diastolic pressure of 95 mm Hg or higher appears to justify the diagnosis of hypertension although the systolic pressure may be below 150 mm Hg

There were 153 males and 73 females which indicates in equal sex distribution since there are about twice as many males as females in our autopsy records for individuals over thirty years of age

The ages at the time of death were as follows thirty four to thirty nine years 2 forty to forty nine years 34 fifty to fifty nine years 49 sixty to sixty nine years 72 seventy years and older 69 cases

The duration of the hypertension cannot be determined from our records but the recorded duration of symptoms is as follows less than one month 5 one to six months 29 six months to one year 20 one to five years 124 five to ten years 35 ten to fifteen years 9 fifteen to twenty years 4 and indefinite 10 cases

In all instances death was due primarily to myocardial failure but there was in some cases a complicating coronary disease or cerebral lesion

The kidneys were normal macroscopically in all instances The condition of the small arteries is shown in Table 52 It may be seen in Table 52 that intimal disease of the renal arteries is somewhat more severe in hypertensive subjects than in the controls

TABLE 5 INTIMAL DISEASE IN THE SMALL ARTERIES IN THE MYOCARDIAL TYPE OF HYPERTENSIVE DISEASE

Controls over 50 yrs	No of cases	Degree of intimal thickening per cent			
1					
A	309	6			
A_1	29	0		—	
4	16	0 9	3 ?	2	
	29	0	1 8	32 0	3
	(	3 4	18	32 3	30
		1 5	20	18	54 0
			26 9	41 4	(5
				? 8	54 4
					32 8

The incidence and degree of arteriolosclerosis in Subgroup A_1 is shown in Table 53 It will be noted that arteriolosclerosis Grades 1 to 3 is four times as frequent in the hypertensive subjects as in the controls but that ?5 per cent show no arteriolosclerosis

TABLE 53 —INCIDENCE AND DEGREE OF ARTERIOLOSCLEROSIS IN THE FOUR MYOCARDIAL SUBGROUPS

	No of cases	Degree of arteriolosclerosis per cent					
		0	1p	1	2	3	1 to 3
Control over 50 yrs of age	312	61 5	22 1	13 4	2 6	0 3	16 3
A_1	226	26 5	6 2	27 4	19 5	20 4	67 3
A_2	16	31 2	6 2	37 5	6 2	18 7	62 4
A_3	29	48 2	10 3	27 6	7 0	7 0	41 6
A_4	67	59 7	7 5	25 4	6 0	1 5	32 9

TABLE 54 —RELATION OF ARTERIOLOSCLEROSIS TO AGE IN GROUP A

Age	Cases	Degree of arteriolosclerosis per cent					
		0	1p	1	2	3	1 to 3
34–49	35	19 4	2 8	47 2	19 4	11 1	77 7
50 59	49	20 0	4 0	30 0	16 0	28 0	74 0
60–69	72	32 0	8 3	13 9	25 0	20 8	59 7
70+	69	29 0	7 2	29 0	16 0	18 8	63 8

Relation of Arteriolosclerosis to Age in Group A_1 —In Table 54 the cases of Group A_1 are arranged by decades and the surprising fact appears that arteriolosclerosis is somewhat less frequent in those over sixty years of age than in the younger age groups

Relation of Arteriolosclerosis to the Level of the Systolic Blood Pressure —In 155 cases in which the maximum systolic pressure was less than 200 mm Hg, the incidence of arteriolosclerosis Grades 1 to 3 was 61 9 per cent and in 71 cases with a pressure above this level arteriolosclerosis was present in 78 9 per cent There is no apparent relation between the incidence of arteriolosclerosis and the size of the heart In 121 cases in which the heart weighed 550 gm or more in females and 600 gm or more in males the frequency of arteriolosclerosis, Grades 1 to 3 was 66 3 per cent, which is practically the average for the entire group

Subgroup A_2 —This group differs from A_1 only in that the weight of

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but they correspond with A_1 in the frequency of vascular disease (Tables 52 and 53) These cases evidently belong with A_1 since it was noted above that there is no correlation between the size of the heart and the degree of vascular disease in the A_1 group

Subgroup A_3 —This group includes 29 cases of cardiac hypertrophy with chronic myocardial exhaustion similar in all clinical features to Group A_1 except that the blood pressure was not recorded In 25 of the 29 cases the heart weighed 500 gm or more It cannot, however, be said with certainty that they are examples of hypertensive disease since the blood pressure is unknown In Table 52 it will be noted that intimal disease of the small arteries is a little more severe than in the controls but slightly less than in the A_1 group In Table 53 it appears that arteriolosclerosis is definitely less than in Group A_1, but much more than in the con

trols These observations indicate that Group A_3 is composed of some cases belonging in A_1 and others that belong in A_4

Subgroup A_4 —This is a series of 69 cases of cardiac hypertrophy and chronic myocardial failure in which the systolic blood pressure was never as high as 150 mm Hg and the diastolic never above 90 mm Hg In most instances the blood pressure was recorded after the onset of cardiac decompensation There was no associated coronary disease In the great majority the blood pressures were recorded several months before death The cardiac weights and the gross anatomical findings at autopsy correspond to those of Group A_1 The frequency and intensity of intimal disease in the medium-sized and small arteries is about the same as in the A series (Table 52) but arteriolosclerosis is only about one-half as frequent (Table 53) When this group is arranged with respect to the level of the systolic pressure the incidence of arteriolosclerosis is as follows 140 to 149 mm Hg 75 per cent of 12 cases 130 to 139 mm Hg 40 per cent of 15 cases below 130 mm Hg 20 per cent of 40 cases Although the number in each group is small there is a suggestion that a pressure of 140 to 149 mm Hg represents hypertension and that these cases belong in Group A_1 In the 40 cases with pressures below 130 mm Hg the incidence of arteriolosclerosis is about the same as in the controls and it is probable that this group represents a form of cardiac hypertrophy and myocardial failure that is not due to hypertensive disease

Group B The Cerebral Type

Headache is a frequent symptom in the early stages as well as throughout the course of hypertensive disease Some patients complain only of headache and this symptom often varies directly with the height of the blood pressure It is probable that headache is often due to increased intravascular pressure within the small cerebral vessels Since these vessels have very little muscle in the media they do not protect the terminal vessels against increases of blood pressure Dizziness is probably due largely to the same cause

Hypertensive Encephalopathy When a patient with hypertension exhibits intense symptoms referable to the brain the condition is sometimes called hypertensive encephalopathy The characteristic features are intense headache convulsions paralyses personality changes and intellectual impairment Renal insufficiency is not a necessary factor Oppenheimer and Fishberg attributed the symptoms to cerebral vasoconstriction but Davison and Brill found sufficient structural changes in the brain to account for the symptoms They found disease of the arteries diffuse areas of demyelination small areas of necrosis and small hemorrhages My observations agree with those of Davison and Brill

Cerebral symptoms are sometimes due to accumulation of a large amount of fluid in the subarachnoid space which causes an increase of intracranial pressure Such patients obtain prompt relief from permanent drainage of the subarachnoid space through a small trephine opening in the skull

In this study a patient with hypertension is classified in the cerebral group if death was due to an apoplectic stroke (hemorrhage or infarction of the brain)

Subgroup B_1 —In this series of 194 cases the systolic blood pressure was 150 mm Hg or higher and the weight of the heart was 350 gm or more in females and 400 gm or more in males There were 123 males and 71 females The age distribution of the entire B group is shown by decades in Table 55 There were 2 cases in the second decade and 3 in the third but 96 2 per cent were over forty years of age at the time of death

TABLE 55 AGE DISTRIBUTION OF THE SEVERAL CLINICAL FORMS OF HYPERTENSIVE DISEASE (AGE AT TIME OF DEATH)

Group	No of cases	Per cent by decades								
		1	2	3	4	5	6	7	8	9 and 10
A	338	0	0	0	1 2	13 0	21 9	30 8	26 6	6 5
B	315	0	0 6	1 0	2 2	13 6	2	29 2	24 1	7 0
C	207	0	0	0 5	1 0	8 7	21 7	4 0	22 2	4 8
D	Males 281	0	0 7	2 5	6 8	25 3	3 6	20 3	7 8	1 0
D	Females 173	0	2 3	4 6	20 8	26 0	16 8	15 6	10 4	2 9

The total duration of the hypertensive state cannot be determined from the available data but it is known that 40 per cent had symptoms for more than one year and 11 per cent for over five years In every case there was a stroke at some time during the course of the illness *The stroke was often the first symptom recognized* by the patient but in many cases the presence of hypertension was recognized many years before the stroke occurred Frequently there were several strokes over a period of years Occasionally there were symptoms of myocardial failure or coronary disease before the fatal apoplectic stroke In about 20 per cent of the cases the first symptom was a stroke and the patient died within one week

In the entire series of Group B (315 cases) there were 290 cases in which the type of brain lesion was known—53 per cent of the lesions were hemorrhages and 47 per cent infarctions

The condition of the small renal arteries in the cerebral group is shown in Table 56 It will be noted that the intensity of the intimal disease is definitely greater in the hypertensive series than in the controls

The involvement of the arterioles in the cerebral group is shown in Table 57 The incidence of arteriolosclerosis is nearly five times that of the controls

Subgroup B_2 —This group comprises 72 cases with hypertension but with a cardiac weight less than 350 gm in females and 400

gm in males Clinically these cases are entirely similar to the B_1 group The involvement of the renal arteries is about the same (Table 56) but the arterioles are a little less severely affected

TABLE 56 —INCIDENCE AND DEGREE OF INTIMAL THICKENING IN THE SMALL ARTERIES IN THE CEREBRAL FORM OF HYPERTENSIVE DISEASE

	No of cases	Degree of lesion 0	1	2	3
Controls over 50 yrs of age	309	0	37 2	32 0	30 [illegible]
B_1	194	0	11 3	31 4	57 2
B_2	72	1 3	11 1	30 6	57 0
B_3	17	0	5 9	58 8	35 3
B_4	11	0	18 [illegible]	2[illegible] 2	54 5
B_5	21	0	14 3	28 5	57 1
Total B	315	0 3	11 4	32 4	55 9

TABLE 57 —INCIDENCE AND DEGREE OF ARTERIOLOSCLEROSIS IN THE CEREBRAL FORM OF HYPERTENSIVE DISEASE

	No of cases	Degree of arteriolosclerosis 0	½	1	2	3	Total 1-3
Controls over 50 yrs of age	312	61 5	2[illegible] 1	13 4	[illegible]	0 3	16 3
B_1	194	16 5	6 7	23 [illegible]	20 6	3[illegible] 5	[illegible]
B_2	72	32 0	5 5	34 [illegible]	8 3	19 4	42 4
B_3	17	6 0	0 0	17 [illegible]	23 4	4 0	94 0
B_4	11	36 4	0 0	36 4	18 2	9 1	63 [illegible]
B_5	21	61 9	0 0	23 8	9 5	4 8	38 1
Total B	315	23 1	5 4	26 3	17 4	2 [illegible]	1 3

In Group B_3 the hearts were large (350 gm or more in females and 400 gm or more in males) but the blood pressures were not recorded

In Groups B_4 and B_5 there was no hypertension In the B_4 group the hearts were hypertrophied and in the B_5 group the cardiac weights were below 350 gm in females and 400 gm in males These three groups are too small for statistical study

Group C The Coronary Type

This subgroup of 207 cases comprises 170 males and 37 females The corrected ratio is about 2 3 males to 1 female The age distribution corresponds with that of the myocardial and cerebral types (Table 55) Nearly 90 per cent of the individuals were over fifty years of age at the time of death (Table 55) In every instance death was due either to coronary sclerosis or thrombosis About 12 per cent died within twenty four hours after the onset of the first coronary attack and about 24 per cent of the patients lived from one day to three months after the first attack About 40 per cent of the patients lived over one year after the disease was recognized and 17 per cent lived over five years Only 2 per cent lived over ten years In many cases hypertension with or

without symptoms of myocardial failure was present for months or years before the occurrence of a coronary attack There is much overlapping between the myocardial, cerebral and coronary forms of hypertension A patient with myocardial failure may develop coronary disease or apoplexy

The 207 [illegible]
in accordai [illegible]
cases) inch [illegible]
and hypertension [illegible]
cardiac hypertrophy [illegible]
Subgroup C_3 (62 ca [illegible]
nary disease but the blood pressures were not recorded Subgroup C_4 (57 cases) had coronary disease and cardiac hypertrophy but no hypertension

The degree of intimal disease in the small arteries is shown in Table 58 In Group C_1 intimal disease is definitely more pronounced than in the controls, but in Groups C_3 and C_4 it is not impressively greater

TABLE 58 FREQUENCY AND INTENSITY OF INTIMAL DISEASE IN THE SMALL ARTERIES IN THE CORONARY TYPE OF HYPERTENSIVE DISEASE

	No of cases	Degree of intimal disease per cent			
		0	1	2	3
Controls over 50 yrs	309	0	37 2	32 0	30 7
C	80	1 3	16 2	40 0	42 5
C_3	62	1 6	30 6	35 5	32 2
C_4	57	3 5	29 8	36 8	29 8

The involvement of the arterioles is shown in Table 59 Arteriolosclerosis *is much more intense than in the controls but it is notably* less severe than in the myocardial and cerebral types of hypertensive disease In the group without an increase of blood pressure (C_4) the incidence of arteriolosclerosis is so low that it appears

TABLE 59 FREQUENCY AND INTENSITY OF ARTERIOLOSCLEROSIS IN THE CORONARY TYPE OF HYPERTENSIVE DISEASE

	No of cases	Degree of arteriolosclerosis per cent					
		0	Ip	1	2	3	Total 1 3
Controls over 50 yrs	309	61 5	22 0	13 6	2 6	0 3	16 5
C_1	80	32 5	12 5	30 0	12 5	12 5	55 0
C_3	62	53 2	3 2	27 4	6 4	9 7	43 5
C_4	57	58 0	12 2	24 5	3 5	1 8	29 8
Total C	199	46 2	9 5	27 6	8 0	8 5	44 1

probable that many of these cases are not hypertensive disease but an *idiopathic form of cardiac* hypertrophy A similar group of the myocardial type without hypertension was discussed above (page 349)

Group D Hypertension With Renal Insufficiency

In about 12 per cent of patients with primary hypertension the kidneys are sufficiently involved to bring about some degree of renal insufficiency. In this study the number with renal insufficiency is much higher because the cases were selected from a much larger group of necropsy records than were the other forms of hypertensive disease. In the 454 cases studied the age distribution is shown in Table 55. It will be noted that in the earlier decades there is a higher percentage of the renal than of the other forms of hypertensive disease and that this is particularly true of the females. The total incidence of renal insufficiency is about the same in the two sexes but the disease occurs more often in young women than in young men. After the age of fifty years the renal type is more frequent in males.

The Duration of Symptoms. Hypertension was known to have been present for over one year in about two thirds of the patients, for over five years in 27 per cent and from 10 to 28 years in 10 per cent. It is almost certain that hypertension was present much longer than the clinical symptoms indicate, especially in the group with a duration of less than one year. It seems impossible for massive cardiac hypertrophy and contracted kidneys to develop within a few months. There is no relation between the known duration of the disease and the degree of cardiac hypertrophy or the extent of the shrinkage of the kidneys. Hypertension is usually not recognized until it produces symptoms. In the great majority of the renal group there is satisfactory evidence that hypertension was present a long time before the onset of renal insufficiency.

tinguish two forms with respect to the onset of uremia, viz acute and chronic uremia. Acute uremia is much less frequent than the chronic form. It is characterized by the rapid development of severe symptoms such as intense headache, very high blood pressure and blindness, and by a rapid increase of blood urea. In the chronic form the blood pressure and the blood metabolites increase slowly over a period of months.

The Blood Pressure.—The blood pressure is usually much higher in the renal than in the other forms of hypertensive disease. In 432 cases in which the blood pressure was recorded the maximum systolic pressures were as follows: 250 to 300 mm Hg 109 cases (25.2 per cent); 200 to 249 242 cases (56 per cent); 190 to 199 19 cases; 180 to 189 25; 170 to 179 12; 160 to 169 8; 150 to 159 4; 140 to 149 9; and below 140 4. The maximum systolic pressure was 200 mm Hg or higher in 81.2 per cent.

When the minimum systolic pressure is used the results are confusing When a patient is under observation for several months or longer the blood pressure may increase as renal insufficiency progresses The pressure may fall to a normal level terminally or as a result of cardiac failure Perhaps the maximum pressure does exaggerate the condition in some instances since in patients with very high pressures a variation of 50 to 70 mm Hg in the systolic pressure may take place within a few hours

There were 4 patients with systolic pressures below 140 mm Hg and diastolic pressures below 80 mm Hg Three of these were terminal pressures in very old persons associated with cardiac hypertrophy The fourth case was a woman 72 years of age with a small heart and coarse renal arteriosclerosis

There were 8 patients with systolic pressures 140 to 144 and diastolic pressures 70 to 88 mm Hg Seven of these had cardiac hypertrophy One patient with a systolic pressure of 140 had a diastolic pressure of 100 mm Hg and cardiac hypertrophy These 8 cases are believed to have had a terminal fall of blood pressure since they had cardiac hypertrophy

The diastolic pressures follow the systolic closely Only in rare instances is there a high diastolic with a normal systolic pressure In about 4 per cent the diastolic pressure was below 90 mm Hg These were the patients with systolic pressures from 140 to 180 mm Hg In 96 per cent the diastolic pressure was 90 mm Hg or higher In about 18 per cent it was 160 to 200 mm Hg

The pulse pressures varied from 45 to 135 mm Hg and about 25 per cent were 100 or higher

With two exceptions the hearts of those with systolic pressures below 160 mm Hg were as large as the average of those with pressures above 200 mm Hg and the kidneys all showed the severe vascular changes characteristic of this group It appears that in rare instances the blood pressure may fall in the terminal stages of hypertensive renal disease probably because of cardiac failure None of my cases was followed sufficiently long to determine whether the low level of pressure prevailed throughout the course of the disease

In a number of instances several blood pressure records are available over a period of years Some examples are as follows the first records being indicated in years before death 168/126 mm Hg one year 220/150 182/106 six years 200/102 234/130 four years 245/150 135/90 six years 210/115 140/80 five years 240/160 140/90 one year 216/130 140/76 six years 220/110 160/110 four years 240/130 150/95 seven years 200/110 170/110 sixteen years 220/130 190/112 six years 230/150 188/90 three years 234/142 155/110 four years 200/170 175/95 ten years 230/160 140/80 five years 188/104 134/94 six years 240/140 The blood pressure may increase gradually over a period of years but

in may increase rapidly or remain stationary There is no relation between the level of the blood pressure and the weight of the heart or the size of the kidneys

TABLE 60 —WEIGHT OF THE HEART IN HYPERTENSION WITH RENAL INSUFFICIENCY

Weight of heart gm	Males		Females	
	Number	Per cent	Number	Per cent
Below 200	0	0	0	0
200 299	0	0	3	1 7
300 399	10	3 6	[illegible]	14 6
400–499	50	17 8	5	30 4
500 599	89	31 8	[illegible]	3 7
600–699	80	8 1	[illegible]	14 6
700 1000	51	18 2	10	5 8
Total	[illegible]		[illegible]	

The Weight of the Heart (Table 60) —In the males 96 4 per cent of the hearts weighed 400 gm or more 78 1 per cent 500 gm or more and 46 3 per cent 600 gm or more The largest heart weighed 1000 gm In the females the average weight is about 75 gm less than in the males 83 5 per cent weighed 400 gm or more 53 1 per cent 500 gm or more and 20 4 per cent 600 gm or more In non hypertensive adults the heart of the male averages about 50 gm heavier than that of the female The greater weight of the male heart is not due to a higher blood pressure since the level of the blood pressure is about the same in females as in males

With respect to age the hearts of the individuals in the second and third decades are smaller but there is no significant relation between the age of the individual and the size of the heart after the age of thirty years In 2 males aged eleven years and eighteen
and
years
ly
renal
group in which there was convincing histological evidence of a high degree of renal insufficiency even when no functional renal tests had been made In 67 of the 454 cases no functional studies had been made and in 11 others the last test made over one month before death did not reveal renal insufficiency In these 78 cases the diagnosis of uremia was based entirely on the structural changes in the kidneys The last determination of blood urea nitrogen in 339 cases was as follows 18 to 29 mg per cent 10 cases (one week to 3 months before death) 30 to 39 mg 14 cases (two days to three months before death) 40 to 49 mg 10 50 to 59 1 60 to 69 mg 1 70 to 99 mg 74 100 to 149 mg 117 150 to 199 mg 64 200 to 299 mg 17 and over 300 mg 3 cases The blood urea increases rapidly during the last few days of life and the high readings (over 100 mg) were usually obtained a few days before death In

several instances it
from about 30 mg
life A similar ra
also in chronic glomerulonephritis

In 25 cases the non protein nitrogen ranged from 32 to 455 mg per cent The two hour excretion of phenolsulphonephthalein ranged from 0 to 44 per cent in 18 cases

Changes in the Kidneys —The combined weight of the kidneys in 448 cases is as follows 50 to 99 gm 2 9 per cent 100 to 199 gm 30 6 per cent 200 to 299 gm 45 5 per cent 300 to 399 17 1 per cent and 400 to 475 gm 3 8 per cent In about one fifth of the cases there is no reduction in the size of the kidneys and only about one third show a severe degree of contraction There is no relation be-



FIG 89 Primary hypertension with chronic uremia Small contracted kidney with a finely granular surface Photograph

tween the weight of the heart and the weight of the kidneys When ... the percentage
the group
h kidneys
weighing 300 gm or more Evidently the duration and intensity of

and on section the cortices are greatly reduced in thickness ...

normal in children or in young adults with acute hypertension

The Small Arteries — These vessels are much more severely affected in the renal than in the other forms of hypertensive disease



Fig 90 Chronic hypertension with acute uremia showing severe intimal fibrosis of a prearteriole Photomicrograph

They show a severe intimal thickening due chiefly to collagen in all cases except those in which uremia is caused by thrombonecrosis In this acute process the severe hypertension is of short duration

Intimal thickening of the small arteries is an important cause of uremia It precedes or accompanies all the arteriolar lesions except widespread thrombonecrosis Sometimes the arterioles are only moderately affected and renal insufficiency is due entirely to narrowing of the small arteries

The Arterioles and Pre-arterioles Three histological types of lesions affect vessels of this size

(a) *Collagenous Intimal Thickening*.—This is the most frequent alteration in the small vessels and it frequently affects the small arteries as well as the pre-arterioles and arterioles. The thickened intima is composed of coarse and fine collagenous fibers (Figs. 90 and 91). In the cases in which uremia develops acutely the intimal fibers are more delicate and more loosely arranged than in the chronic uremias in which the fibers are coarser and more compact.

Collagenous intimal thickening was present in some degree in about 85 per cent of the kidneys and in about 70 per cent it was of severe degree (Grades 3 and 4). In about 3 per cent it was the only lesion in the vessels but the severe lesions (Grades 3 and 4) were associated with hyaline degeneration in 24 per cent, with thrombonecrosis in 25 per cent, and with both of these lesions in 47 per cent.

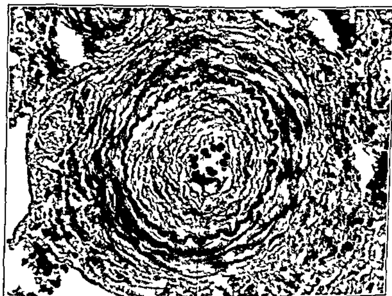


Fig. 91.—Chronic hypertension with acute uremia (malignant hypertension) showing intimal fibrosis of a small artery. Photomicrograph.

Hyaline Degeneration.—This lesion in its pure form consists of a subintimal deposit of homogeneous material (Fig. 86) but it blends with the coarse collagenous type frequently. The coarse fibers become fused and present a hyaline appearance. On the other hand subintimal hyalin frequently becomes denuded of its endothelial ... of a thrombus. The separation ... thickening

Hyaline degeneration was the most important ... tion in the

arterioles in about 15 per cent of the kidneys and some hyaline material was recognizable in about two-thirds of the kidneys.

Thrombonecrosis.—This lesion consists of a thrombosis of the arterioles with or without necrosis of the arteriolar wall. In most instances degenerative changes in the arteriolar wall are not con-

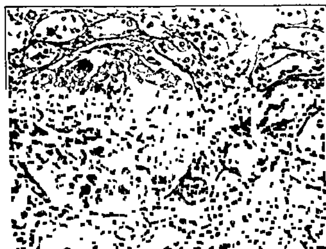


Fig. 92.—Chronic hypertension with acute uremia (malignant hypertension) showing thrombonecrosis of afferent arteriole. Photomicrograph.



Fig. 93.—Chronic hypertension with acute uremia (malignant hypertension) showing thrombonecrosis of afferent arteriole and acute glomerulitis.

spicuous and the lesion may be described as a simple thrombosis but sometimes the entire arteriole is obviously necrotic (Figs 92 93) Thrombonecrosis is very rarely the sole cause of uremia since it does not involve all of the arterioles It is associated with collagenous intimal thickening and hyaline degeneration In 15 per cent of the kidneys a majority of the arterioles were thrombosed (Grades 3 and 4) in 50 per cent occasional arterioles were involved and in 35 per cent there were no thrombosed arterioles

Arteriolar thrombosis is not restricted to the renal type of hypertensive disease but it is more frequent and more extensive in this condition Occasional thrombosed arterioles are found in some cases of glomerulonephritis as well as in some instances of the cerebral myocardial and coronary types of hypertensive disease

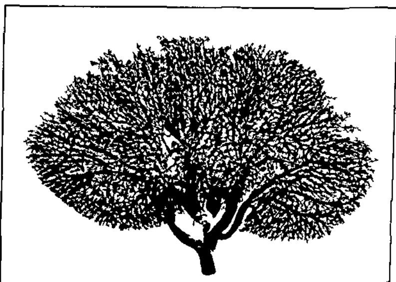


FIG 94 Normal kidney injected under a pressure of 600 mm Hg Prepared by Dr Harry Wilmer

Focal Glomerulitis —One of the features of hypertension with renal insufficiency is the frequent occurrence of focal glomerulitis This is an exudative and proliferative lesion in the glomerular capillaries occurring usually in only a small percentage of the glomeruli (Fig 93) Focal glomerulitis was found in 35 8 per cent of the kidneys of this series In 29 6 per cent only occasional glomeruli were affected (Grade 1) in 4 5 per cent frequent glomerular lesions were observed and in 1 7 per cent the lesions were so numerous that they contributed materially to renal insufficiency As noted above the capillaries of the glomeruli contain many leukocytes and show some endothelial proliferation There is

always a severe involvement of the afferent arteriole of the affected glomerulus

Changes in the Renal Parenchyma.—One of the striking effects [illegible]

Figures 94 and 95

In the great majority of the kidneys hyaline glomeruli are a conspicuous microscopic feature; in the small contracted kidneys they are nearly all hyaline. The atrophy of the glomeruli is due to a fibro-hyaline obliteration of the prearterioles and arterioles. In the larger kidneys the number of hyaline glomeruli is much less. In 13

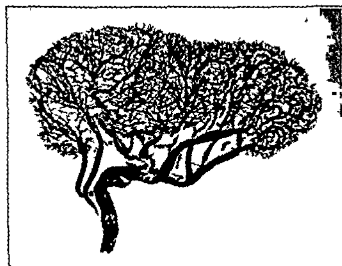


Fig. 95.—Kidney weighing 190 gm from a case of [illegible] uremia. Note the dilated tortuous arteries and the [illegible]ration of many small vessels. Injected under a pressure of 600 mm Hg. Prepared by Dr Harry W [illegible]

kidneys there were no hyaline glomeruli, these being chiefly large kidneys in which uremia was due mainly to thrombonecrosis or [illegible]

to acute changes in the arterioles and prearterioles

In 18 cases atrophy of the cortex was caused by severe narrowing of the medium-sized arteries, the smaller vessels being only moderately affected. This group is clearly a chronic uremia with no acute changes.

In about two-thirds of the cases the principal lesion is in the small

arteries and consists of collagenous and elastic intimal thickening which appears to be a continuation of a similar change in the intima of the larger arteries This is a chronic process and it brings about a progressive atrophy of the renal parenchyma In the majority of this group there are also some acute lesions in the arterioles, viz, thrombonecrosis, glomerulitis, or loose fibrous intimal thickening There is therefore a terminal acute process superimposed on the chronic vascular disease



FIG 96 —Chronic hypertension with chronic uremia Note collagenous and hyaline changes in the arteries and arterioles hyaline glomeruli and atrophic tubules. Photomicrograph

In 40 cases the principal lesion was hyaline degeneration of the *arterioles as* [illegible] This
differs from [illegible]
tensive disease only in its greater [illegible]
or no acute changes in the arterioles in this group

In 40 cases the principal cause of uremia was thrombonecrosis of the arterioles and prearterioles Some thrombonecrosis was found in about two-thirds of the entire group, but in these 40 cases it was the outstanding lesion Often these were large kidneys *with few or no hyaline glomeruli*

In what respects do the vascular lesions in the renal type differ

females

In the non-renal forms of hypertensive disease the lesions in the small vessels are chiefly hyaline and fibro-hyaline and only a few arterioles are completely closed. In 40 cases of my series with renal insufficiency the arteriolar lesions were of the hyaline type and differed only in intensity from those of non-renal hypertension, and in 24 other cases the arterioles were not severely involved, the uremia being due to a severe intimal thickening of medium-sized and small arteries. It may be said therefore that in 64 cases of this series the vascular lesions differ only quantitatively from those of non-renal hypertension.

Thrombonecrosis is, however, a distinctive lesion. An occasional arteriole with thrombonecrosis may be found in a small percentage of cases of non-renal hypertension, but the lesions are never conspicuous except in the renal form. Thrombonecrosis was the principal cause of uremia in only 40 of 454 cases (9 per cent) but the *lesion was present in a few vessels in 65 per cent of this series.* It cannot be said that thrombonecrosis is an essential feature of malignant hypertension since it is entirely absent in one-third of the

was present

of uremia in

appear loosely arranged as though separated by fluid (Figs [illegible]) In the nonrenal forms of hypertensive disease the intima of these vessels is composed of coarse fibers and hyalin.

It may be concluded that in 64 of the 454 cases of this series the vascular lesions are similar to those of non-renal hypertension except in their greater intensity, but in the remaining 390 cases the histological structure of some of the lesions is sufficiently different to

indicate a different etiological factor It is clear that the great majority of the patients who finally die of uremia suffer for months or years of h merto

ciency

are basica

imposed influence brings about the distinctive changes in the small renal vessels

Malignant Hypertension —This term was introduced by T Fahr to designate primary hypertension with uremia He considered malignant hypertension a distinct disease pointing out that it is more common in younger individuals and in females and that the lesions in the small arteries and arterioles are distinctive Lohlein and others at that time disagreed with Fahr s interpretation and considered malignant hypertension merely as an advanced stage of ordinary hypertension

In recent years the majority of writers have agreed with Fahr that malignant hypertension is a special disease (McMahon Kimmelstiel and Wilson) but they have usually restricted the concept to hypertension with acute uremia the diagnosis being based on the structural changes in the small arteries and arterioles If a pa

majority of
the vascular
mbonecrosis

On the other hand many clinicians follow Keith and Wagener who diagnose malignant hypertension by the retinal changes edema of the disks sclerosis of arteries hemorrhages and cotton wool exudates In the 88 cases studied by Keith and Wagener all had very high blood pressure 21 had fairly normal renal function

rhages

Hypertensive retinitis is the effect of high blood pressure in the retinal vessels It does not depend directly upon renal insufficiency since renal insufficiency without hypertension is not associated with retinitis The reason that retinitis is nearly always present in

that
even
erva

tions of Keith and Wagener

If we use malignant hypertension in the sense of hypertensive

retinitis it includes nearly all cases with renal insufficiency and a few with fair renal function. Anatomically it obviously includes both the chronic hyaline and the acute vascular lesions.

It is perhaps best to use "malignant" hypertension in an anatomical sense to include only those cases which show prominently the acute renal lesions described above, i.e., thrombonecrosis, intimal fibrosis and glomerulitis. Clinically this would include patients with hypertension who develop a very high blood pressure and hypertensive retinitis and pass into uremia rather rapidly.

If we use "malignant" hypertension in the anatomical sense just described it becomes a fairly well-defined entity to the pathologist although there are some borderline cases. The lesion differs sharply from ordinary hyaline arteriolosclerosis. The nature of the lesion in the small vessels is obscure. Schurmann and McMahon regard the lesion as an arteritis and compare it to periarteritis nodosa. As pointed out by Fahr, a relatively large proportion of the cases of malignant hypertension occur in young individuals and in females and there is therefore some clinical evidence of a distinct disease.

The Relation of Renal Arteriolosclerosis to Hypertensive Disease.—In Table 61 the incidence and degree of arteriolosclerosis is shown in the different clinical forms of hypertensive disease. The arterioles are diseased in all cases of the renal group. In the myocardial, cerebral and coronary groups only those cases are tabulated in which it was known that the patient had high blood pressure. The percentage with definite arteriolosclerosis (Grades 1 to 3) is smaller in the coronary than in the other forms. Nearly 25 per cent of all individuals with typical clinical hypertensive disease of the non-renal types have normal renal arterioles (Grade 0) and about 7 per cent have only occasional hyaline deposits in the arterioles (Grade 1_p).

TABLE 61.—INCIDENCE OF ARTERIOLOSCLEROSIS IN THE DIFFERENT CLINICAL FORMS OF HYPERTENSIVE DISEASE

	No. of cases	Degree of arteriolosclerosis, per cent: 0	1_p	1	2	3	Total 1–3
Controls over 60 years of age	300	61.5	2.0	13	2.6	0.3	16.5
Myocardial (A_1, A_2)	21	26.9	6.–	28.1	18.2	20.2	66.5
Cerebral (B_1, B_2)	26	20.–	8.4	26	1.3	29.0	3.0
Coronary (C)	60	32.5	1.5	30.0	12.5	12.5	55.0

Castleman and Smithwick examined biopsies from the kidneys of 100 hypertensive patients, the specimens being taken at the time of sympathectomy operations. Using the criteria of Moritz and Oldt (which includes pre-arterioles) they found no vascular disease in 7, Grade 1 lesions in 21, Grade 2 in 25, Grade 3 in 33 and Grade 4 in 14 patients. These observers believed that in a fairly high percentage the vascular lesions are an inadequate explanation of the hypertension.

It cannot be maintained that hypertension is always caused by renal arteriolosclerosis since the arterioles are often normal or only slightly affected. If one includes the pre-arterioles with the arterioles the percentage of involvement is higher (Table 62) but there remain 17.5 per cent in which both arterioles and pre-arterioles are normal. As regards the small arteries, these vessels are somewhat more severely affected in the hypertensive subjects than in the controls (Table 46) but all the controls show intimal disease and in about one-third of them the lesion is severe (Grade 3). In many of the patients with renal insufficiency these arteries are so markedly narrowed that they cause atrophy of the renal cortex. Lesions of this degree (Grade 4) [illegible]

of the cortex

TABLE 62.—INTIMAL DISEASE OF PRE-ARTERIOLES IN THE CONTROL GROUP AND IN THE NON-RENAL FORMS OF HYPERTENSIVE DISEASE

	No of cases	Per cent					
		0	1p	1	2	3	Total 1-3
Controls over 50 years	309	52.1	24.0	20.1	3.2	0.6	23.9
Myocardial A_1	226	19.9	4.0	24.3	25.7	26.1	76.1
Cerebral B_1	194	11.3	5.7	22.7	19.6	40.7	83.0
Coronary C_1	80	25.0	6.2	37.5	8.7	22.5	68.7

It must be admitted therefore that clinical hypertension may develop in persons in whom the pre-arterioles and arterioles are normal and the small arteries no more severely affected than in the non-hypertensive controls. In other words hypertension may develop in persons whose renal vascular lesions are no greater than is found in non-hypertensive controls.

However, when the renal vascular lesions are sufficiently severe to cause renal insufficiency a very high blood pressure is almost invariably found and the evidence seems convincing that severe vascular renal lesions almost always cause the blood pressure to rise to higher levels.

We may conclude that hypertension may develop in the absence of renal vascular disease but that severe involvement of the small renal arteries and arterioles causes the blood pressure to rise to higher levels and in exceptional acute cases may initiate the hypertension.

Since 16.5 per cent of the non-hypertensive controls show moderate arteriolosclerosis it is obvious that moderate arteriolar disease does not cause hypertension. Intimal thickening of the arteries and arteriolosclerosis are age changes that do not affect the blood pressure until they become severe.

Since arteriolosclerosis is more severe and more frequent in hypertensive subjects than in non-hypertensive controls one must conclude that there is some causal connection between the condition

of the arterioles and the level of the blood pressure. We may believe that hypertension accelerates the age changes in the renal vessels because of the greater strain on the arterial wall. When ever the arterioles become severely affected either as a result of age changes because of the strain of chronic hypertension or by some acute vascular disease the blood pressure rises above its previous level.

The theory that hypertension and renal arteriosclerosis are independent diseases that intensify one another is consistent with our present knowledge.



Fig 97 Retina from a case of hypertension [illegible] and ve[illegible] The artery shows a moderate thickening of [illegible] wall [illegible] arteries also [illegible] Retinal arteries of this size normally [illegible] other change [illegible] entirely of collagen. The vein shows [illegible] change. Photomicrograph [illegible] composed

Retinal Changes in Hypertension. In chronic hypertension the most common change in the eyegrounds is an irregular narrowing of the small retinal arteries with an increased light reflex and narrowing of the veins at the arteriovenous crossings. This narrowing of the arteries is usually interpreted as angiospasm but it persists

indefinitely (Bordley and Eichna), and if it is spastic it must be a permanent spasm. *The narrowing of the vessels in eclampsia* is presumably spastic since it disappears, but most observers agree that the vessels in primary hypertension remain contracted permanently. The nature of this contraction is not understood anatomically. Vessels of this caliber in the retina have few or no muscle fibers in their walls, the media being composed almost entirely of collagen. Unless collagenous tissue can contract angiospasm is not possible in these vessels. When examined micro-



Fig 98.—Choroidal arteriole in hypertensive retinitis. Note the hyaline intimal thickening. These vessels are not seen in the fundus examination. Photomicrograph.

scopically these arteries differ very little from the normal, but the collagenous media is often somewhat thickened (Fig 97). It is *possible that there is narrowing* of the muscular arteries in the nerve head and that the visible vessels appear smaller because they contain less blood.

Whether the hypertension be of the primary type or due to chronic glomerulonephritis a very *high blood pressure* usually

brings about a hypertensive retinitis The most characteristic early change in hypertensive retinitis is papilledema with a gradual spread of the edema out into the retina and congestion of the veins (Keith Wagener, and Kernohan) The edema of the retina becomes more severe and hemorrhages and cotton wool patches appear Hypertensive retinitis is apparently due to the unusually high pressure in the retinal vessels It is usually associated with renal insufficiency since these are the patients with very high blood pressure but hypertensive retinitis was observed in 7 cases of our series with blood pressures about the level of 230 140 mm Hg but without any renal insufficiency It is the height of the blood pressure and not uremia which causes retinitis

The choroidal arteries have the same histological structure as arteries of corresponding size elsewhere and in hypertension they show hyaline intimal changes such as are found in the kidneys (Fig 98)

The Arteries of the Brain —Since the small arteries and arterioles of the brain like those of the retina have very little smooth muscle

This may be the reason why headache is such a frequent symptom

In hypertension without renal insufficiency there are few or no *changes in the small cerebral arteries* and arterioles but in hypertension with retinitis or uremia one finds thickening and reduplication of the elastica interna of the small arteries and hyalinization of the media with intimal atherosclerosis of the larger vessels (Baker)

THE ETIOLOGY OF PRIMARY HYPERTENSION

The boundary between normal blood pressure and hypertension is ill defined and there are innumerable transitions between low

due to overaction of some mechanism that maintains normal pressure or whether it is caused by a different factor resulting from disease of some organ or tissue

Mechanisms Concerned in the Regulation of the Blood Pressure —The several organs or physiological mechanisms which may influence the blood pressure are as follows (*a*) the heart (*b*) the carotid sinuses and the depressor nerves (*c*) the large elastic arteries (*d*) the vasomotor center and vasomotor nerves (*e*) the adrenal glands (*f*) the kidneys and (*g*) the small muscular arteries and arterioles

(*a*) **The Heart** —The work required to maintain the systemic blood pressure is furnished by contractions of the left ventricle

which propel blood into the aorta The level that the blood pressure reaches depends upon the peripheral resistance and the force of the ventricular contractions If the peripheral resistance be decreased the blood pressure falls although the heart is working normally *On the other hand if the* peripheral resistance be increased the heart reacts with stronger contractions and increases the blood pressure This response on the part of the heart is probably a reaction to the increased load and it is compensatory in the sense that the increased work maintains the minute volume output and thereby furnishes the normal amount of blood to the tissues *In nearly all forms of hypertension the diastolic pressure* is increased indicating increased peripheral resistance

When the heart muscle is weakened from disease such as infarction from coronary thrombosis or anemia or myocardial fibrosis from coronary atherosclerosis the blood pressure may be decreased because the weakened myocardium is unable to maintain it at a high level *Myocardial disease in a patient with primary hyper*tension frequently causes the blood pressure to fall to lower levels even though there is no decrease in the peripheral resistance It must be emphasized that a strong cardiac muscle is necessary to maintain a high blood pressure

When the nutrition of the cardiac muscle is good it responds to *increased peripheral resistance by more forceful contractions* and the increased work brings about hypertrophy of the left ventricle

[illegible]

quacy of the coronary circulation the age of the individual the debilitating effects of associated diseases and other factors that are unknown

In about one half of the clinical cases of primary hypertension the cause of death is myocardial exhaustion but this is a result of the strain imposed on the heart by the increased peripheral resistance There is no evidence that any form of hypertension is a primary disease of the heart All of the therapeutic procedures by which the blood pressure may be temporarily decreased act by reducing the peripheral resistance and not by weakening the myo[illegible] pro-

[illegible]

tissues would receive less blood

(*b*) **The Carotid Sinuses and the Depressor Nerves** — *This is a very* important mechanism for the regulation of blood pressure The nerve endings in the walls of the carotid sinuses are sensitive to chemical stimuli and to differences of intravascular pressure increases of pressure causing reflex slowing of the heart and decreases permitting increased cardiac contractions Pressure on a carotid

sinus in many individuals causes a temporary slowing or cessation of the heart beat and a temporary decrease of blood pressure (Mandelstamm and Lifschitz) This effect is attributed chiefly to stimulation of the depressor nerves to the heart, but there is probably some peripheral relaxation of arterioles also

In the rabbit the cardiac depressor nerves are separate from the vagus Mies, 1932 sectioned the depressor nerves in rabbits and produced chronic hypertension Nowak produced chronic hypertension in dogs by removal of both common carotid bifurcations [illegible] ervation of the [illegible] cal sympathec- [illegible]

There is no doubt that chronic hypertension may be produced in animals by interruption of the depressor nerves but there is no evidence at present that clinical hypertension rests on this basis The animal with this form of hypertension has tachycardia which is not present in clinical hypertension Nevertheless it is a mechanism that helps to regulate normal blood pressure and it is conceivable that some chemical substance in the blood depresses the carotid sinus reflex

(c) **The Large Elastic Arteries** —The function of the large arteries is indicated by the high proportion of elastic tissue in their walls They distend to accommodate the blood forced in at each ventricular systole and by their elasticity maintain a steady flow of blood into the arterioles That they do not normally offer a great deal of resistance to the flow of blood is indicated by the fact that the first marked fall of pressure occurs in the small peripheral vessels

There is a progressive loss of elasticity of these vessels with advancing age due to degeneration of the elastic tissue and some degree of ectasia of the aorta and its large branches is fairly constant in advanced life Intimal atherosclerosis is almost uniformly present in advanced life Atherosclerosis does not materially reduce the size of the lumen of the aorta and its large branches but it produces narrowing of the smaller arteries such as the coronary and cerebral arteries Atherosclerosis is usually somewhat more [illegible]

in advanced life increase the work of the heart or tend to elevate the blood pressure? Fahr Davis and Spittler using the Starling heart lung preparation and varying the elasticity of the system by air chambers came to the conclusion that increased rigidity of the system does not increase the work of the heart They found that the diastolic pressure fell more than the systolic rose Wiggers noted that in hypertension there is a high pulse pressure which he attributes to decreased elasticity of the large arteries and a high diastolic pressure referable to narrowing of the small peripheral

vessels He believes that rigidity of the large arteries causes some increase of cardiac work and tends to raise the systolic pressure All observers are agreed that the chief cause of hypertension is not in the large arteries but in the small peripheral vessels

Some persons over sixty years of age have an increase of systolic pressure and pulse pressure but no increase of diastolic pressure This systolic hypertension is probably due to rigidity of the large arteries and it may not be the same disease as diastolic hyper tension

Coarctation of the Aorta —In this well known disease there is a congenital stenosis of the aorta immediately below the origin of the left subclavian artery The blood reaches the abdominal aorta by a circuitous collateral circulation through the intercostals and *internal mammary arteries In the upper extremities there is* nearly

and us

but in

creased In the legs the systolic pressure is seldom over 125 mm Hg and the diastolic is usually found to be increased when the pressure is determined by direct intravascular measurement Steele with a needle in the femoral artery found that the pulse pressure in the femoral was only 11 to 15 mm Hg and the diastolic pressure nearly as high as in the arms The diastolic pressure in the arms was 120 to 130 mm Hg and in the femoral artery 108 to 120 mm Hg There is apparently a general increase of peri pheral resistance in most instances as indicated by the increased diastolic pressure in the legs as well as the arms

There is disagreement in the literature as to the cause of this hypertension Prinzmetal and Wilson thought that the hyper tonus in the upper extremities is of vasomotor origin since they found that heat causes a very marked increase of blood flow in the arm Friedman and associates measured the renal blood flow in 6 cases of coarctation In each case they found a normal inulin clearance and a moderate reduction of the diodrast clearance indicating a partial renal ischemia This could be explained on the assumption that there is an increased tonus of the efferent glomerular arterioles

Brotchner applied a clamp to the abdominal aorta of dogs at different levels and measured the blood pressure by a cannula in the carotid artery When the clamp is applied above the origin of the celiac ax

blood pressure

the increase of

when the clamp is below the renal arteries Complete clamping of the aorta causes a more marked rise of pressure than a partial constriction The blood pressure returns to normal immediately after the clamp is released

This acute experimental hypertension develops too rapidly to be an effect of a humoral agent liberated from the kidneys or any other organ. It is probably due simply to mechanical obstruction of the aorta.

Page constricted the aorta of dogs immediately below the diaphragm. No chronic hypertension was obtained apparently because of the development of collateral circulation. The clinical picture of coarctation has not been produced in animals.

Maycock reported a case of coarctation of the aorta below the level of the renal arteries in a girl aged eighteen years with chronic hypertension. In this instance there can be no argument for renal ischemia.

Is the hypertension in coarctation due to mechanical factors or to a pressor substance in the blood? In the acute hypertension produced by Brotchner and in Maycock's clinical case renal ischemia may be excluded and the hypertension must be attributed to mechanical obstruction of the aorta and consequent increased load on the heart. The decreased renal blood flow observed by Friedman may be due to the circuitous route through small vessels which the blood must travel to reach the kidneys rather than to a pressor substance in the blood. Coarctation bears some similarity to aortic stenosis since the obstruction is not very far from the left ventricle. No one would attribute the left ventricular hypertrophy and intraventricular hypertension of aortic stenosis to renal ischemia.

(*d*) **The Vasomotor Center and the Vasomotor Nerves.** The vasomotor center in the brain exerts a controlling influence on the blood pressure through the vasomotor nerves which supply the smooth muscle in the walls of the arteries and arterioles. This is one of the most important mechanisms for the regulation of the blood pressure. Stimulation of the sympathetic nerves of an organ causes contraction of its arterioles and section of the nerves causes dilatation and hyperemia of the tissue. After cervical sympathetic ganglionectomy the arm immediately becomes warm and flushed and there is an increased blood flow. The hyperemia persists for several weeks but slowly returns to normal. A similar hyperemia occurs in the leg after lumbar sympathetic ganglionectomy. The increased blood flow is chiefly in the hands and feet.

In a normal extremity warming of the body causes an increase and cooling a decrease of blood flow, but these reactions do not occur in a sympathectomized limb.

After destruction of the spinal cord there is an immediate generalized decrease of tone in the arterioles and the blood pressure falls to a low level.

These experimental observations indicate that the vasomotor system plays a major role in maintaining the tone of the peripheral

vessels and sustaining the blood pressure It is believed that an increase or decrease in tonus over the greater part of the body is necessary to elevate or lower the blood pressure Sympathectomy of one extremity does not affect the blood pressure In hypertension it is not known whether the increased vascular tonus involves all parts of the vascular system to the same degree or whether increased tone in the splanchnic area alone is sufficient to increase the blood pressure The paucity of muscle fibers in the arterioles of the brain suggests that there may even be hyperemia of the brain in *hypertension and the frequency of headache in hypertensives* supports this view

Prinzmetal and Wilson studied the blood flow in the arm by means of a plethysmograph In 4 normal controls and in 5 persons with hypertension they found the blood flow in the arm about the same They concluded that there is hypertonus in the arms in hypertensive subjects Abramson however found a much greater blood flow in the arms of hypertensive persons and concluded that the hypertonus is not in the arms but elsewhere

After injection of the sympathetic ganglia with novocaine Prinzmetal and Wilson found no greater increase of blood flow in the arm in the hypertensives than in the normal controls They concluded that the increased hypertonus in the arms in hypertensives is not of vasomotor origin Wilkens found that sympathectomy does not increase the blood flow to the muscles of the calf of the leg in hypertensive subjects Rhoads and his associates found that denervation of the kidneys in dogs did not increase the renal blooc [illegible] of renal blood flow [illegible] the kidneys

Ste[illegible] cts in which a marked temporary fall of blood pressure [illegible] produced by malaria therapy [illegible] the same when th[illegible] 150/110 mm Hg [illegible] the basic peripheral resistance These observations indicate that

[illegible]

only a slight transitory hypertension but ligature of the superior mesenteric causes a persistent elevation of blood pressure However this hypertensive effect may be due to the nearness of the obstruction to the heart rather than to the region supplied by the ligatured vessel

Sympathectomy for Primary Hypertension —Several operations have been devised for denervating the abdominal viscera Anterior spinal nerve root section is considered effective but too dangerous

The supradiaphragmatic operation consists of bilateral splanchnic nerve resection with lower dorsal ganglionectomy. Some favorable results have been reported but the outcome is usually disappointing.

Subdiaphragmatic sympathectomy has been practiced chiefly at the Mayo Clinic (Allen and Adson). This operation consists of bilateral resection of the splanchnic nerves, celiac ganglia and the two upper lumbar sympathetic ganglia. In a group of 224 patients Allen and Adson report the result as good in 13 per cent, fair 18 per cent, temporary 39 per cent and poor 30 per cent. A prolonged reduction of blood pressure is considered a good result.

The more extensive Smithwick operation is said to give the best results. The minimal Smithwick operation consists in removal of the sympathetic ganglia from the tenth thoracic to the first lumbar inclusive, the maximal operation from the sixth thoracic to the third lumbar inclusive. When the second lumbar ganglia are removed the legs are denervated. Smithwick reported good results in a majority of 156 patients. The result is not related to the degree of renal arteriolosclerosis found by biopsy of the kidneys. The most striking improvement is in the eyegrounds. A successful denervation produces orthostatic hypotension. None of the patients had renal insufficiency. Denervation of the kidneys does not increase the renal blood flow.

There is agreement that in many patients sympathectomy produces clinical improvement. Headache is less troublesome and frequently vision is much improved because of disappearance or decreased intensity of the retinal lesions. The blood pressure is often notably reduced and may remain permanently lower but it often returns to the preoperative level. There may be subjective improvement without a reduction in blood pressure. There is no improvement in renal function and there is no significant change in the renal blood flow.

Since the renal blood flow is not increased the beneficial effects of sympathectomy cannot be attributed to a decreased tonus of the renal arterioles and it may be inferred that there is no vasomotor spasm in the kidneys in primary hypertension. When a normal individual changes from the recumbent to the upright posture there is increased vasomotor tone in the abdominal visceral arterioles which prevents an undue accumulation of blood in this region which would otherwise result from the sudden increase of hydrostatic pressure. A bedridden patient may faint upon assuming the standing position since he is unable to make this adjustment and develops anemia of the brain. Shortly after abdominal sympathectomy the hypertensive patient may likewise faint upon standing unless the abdomen is supported by a bandage. In the course of time the visceral arterioles regain their tonus to a large extent but after sympathectomy many hypertensive subjects have a lower blood pressure when standing than when recumbent.

What is the mechanism by which sympathectomy effects a lowering of the blood pressure? The orthostatic hypotension seems sufficient evidence that the vasomotor tonus of the arterioles in the abdominal viscera and after the more extensive operations in the arterioles of the lower extremities also is largely abolished by sympathectomy This is satisfactory evidence that the tonus of the visceral arterioles in hypertensive subjects is at least in part vasomotor in origin but it does not prove that there is an increased vasomotor tonus in this region in hypertension Sympathectomy may merely remove the normal vasomotor tonus

LI J

lower the blood pressure to some extent

When a hypertensive patient is kept quietly in bed the systolic pressure often falls 20 to 30 mm Hg and the diastolic decreases also except in persons with renal insufficiency In testing any therapy for hypertension the effect of bed rest must be taken into account

falls slightly
I to 40 mm
decrease of
the diastolic Upon awakening the pressure quickly returns to

marked reactions than normal persons to vasomotor stimuli Hyper ventilation (low CO to the brain) has no effect on a normal blood pressure but causes a marked fall of blood pressure in a hyper tensive subject Likewise the vasopressor response to inhalation of carbon dioxide is much greater in hypertensive elderly persons

il falls of blood pressure in
esthesia The fall was as
ith no renal insufficiency
They believe there is a vasomotor tonus even in those with uremia

In many hypertensive subjects there are marked variations in the level of the blood pressure from time to time The percentage variation in the diastolic pressure is about the same as in the systolic Patients with hypertension do not have a fixed diastolic pressure (Ayman)

The vasomotor system is therefore very important in primary hypertension although it is apparently not the site of the basic

disturbance. Extensive sympathectomy is often beneficial because it removes from a large part of the vascular bed one of the influences which increase the tonus in the arterioles.

Increased Intracranial Pressure. In the Cushing experiment a cannula is inserted into the subarachnoid space through a small trephine opening in the skull. The cannula is then connected to a flask containing a fluid such as warm physiological salt solution. By raising or lowering the flask any desired level of intracranial pressure may be obtained. The blood pressure, measured by a cannula in the carotid artery, rises immediately when the intracranial pressure approaches the level of the systolic blood pressure and falls very rapidly when the intracranial pressure is lowered. Increased intracranial pressure produces only a slight rise of blood pressure in the dog after denervation of the heart and denervation or removal of the adrenals. Presumably the stimulus reaches the heart via the adrenals (Freeman and Jeffers).

The only clinical parallel to the Cushing experiment is a massive subarachnoid hemorrhage which usually produces acute hypertension. In the Cushing experiment the blood pressure does not rise very much until the intracranial pressure is nearly as high as the systolic blood pressure and apparently transudates and exudates in the subarachnoid space seldom produce such high pressures. Brain tumors do not cause hypertension (Wilson) and it is seldom that the blood pressure increases after an intracranial hemorrhage, because these lesions do not produce a uniform increase of intracranial pressure.

It is believed that intracranial pressure acts by producing ischemia of the vasomotor center. Several investigators have attempted to explain primary hypertension on the basis of anemia of the vasomotor center from sclerosis and narrowing of the arteries of the brain but the anatomical evidence is inadequate. Nowak and Walker produced chronic hypertension experimentally by progressive occlusion of the cerebral arteries.

(e) **The Adrenal Glands.**—The adrenals produce pressor substances in both the cortex and the medulla. In adrenal insufficiency (Addison's disease) the blood pressure is usually but not invariably decreased. The systolic pressure seldom falls below 100 mm. Hg. Epinephrine produces a sharp transitory hypertension. The chromaffin cell tumors of the medulla produce paroxysmal attacks of severe hypertension. These tumors contain large amounts of epinephrine which is apparently liberated into the blood stream at irregular intervals. Adenomas and carcinomas of the adrenal cortex often produce a moderate chronic hypertension (Cushing's syndrome).

In experimental renal as well as in experimental neurogenic hypertension (page 381) adrenalectomy abolishes the hypertension. There is not much evidence to incriminate the adrenals in clinical

primary hypertension since there is no adrenal hypertrophy, the blood sugar is normal and hypertensive patients react to epinephrine as normal individuals do However the disturbance of renal function in primary hypertension seems to be due to increased *tonus of efferent glomerular arterioles*, and it is known that this may be produced by minute injections of epinephrine There is [illegible]

contain a pressor substance and a majority of renal diseases are attended with hypertension The association of renal disease with hypertension is so frequent that many observers attribute primary hypertension to a renal disorder

(1) *Diffuse Glomerulonephritis* —With rare exceptions all forms of glomerulonephritis acute subacute and chronic are attended with hypertension Hypertension may be absent in mild acute cases Rarely chronic cases without hypertension are reported The blood pressure is only moderately elevated in mild or latent chronic cases and it tends to become higher *with the development* of definite renal insufficiency In advanced chronic cases the blood pressure is often as high as in primary hypertension with uremia

In glomerulonephritis there is extensive obstruction of the glomerular capillaries and presumably a marked reduction in renal blood flow

(2) *Lipoid Nephrosis* —In the pure type of lipoid nephrosis there is no obstruction of the glomerular capillaries and these cases do not exhibit hypertension However, when the capillary basement membranes are sufficiently thickened to produce some narrowing of the glomerular capillaries a moderate hypertension develops In the cases that progress to uremia nearly all the capillaries are very narrow or completely obstructed and the blood pressure is as high as in glomerulonephritis We may therefore, *conclude* that the same mechanism is operative in lipoid nephrosis as in glomerulonephritis

(3) *Polycystic Kidneys* —In a group of 108 cases of bilateral polycystic kidneys collected from the literature and my own experience I found t [illegible] 150 mm. Hg or higher [illegible] occurs in [illegible] patients [illegible] relation between the stage of the disease [illegible] many have uremia without hypertension The numerous cysts in the kidney compress the persistent parenchyma and presumably there is ischemia of the areas that have not undergone atrophy It is possible that those without hypertension have some areas of parenchyma well supplied with blood

(4) *Hydronephrosis* —In a study of 1031 cases of hydronephrosis

There is clinical evidence that acute obstruction of one or both ureters often causes a transitory hypertension. Experimentally one may produce acute hypertension in animals by obstructing both ureters (Harrison, *et al.*) but no one has succeeded in producing chronic hypertension by hydronephrosis. From anatomical considerations it seems certain that there is a decreased blood flow in hydronephrotic kidneys but chronic hypertension seldom develops.

(5) *Bilateral Renal Hypoplasia.*—Bilateral renal hypoplasia does not cause hypertension. In our case (page 70) there was a very small amount of normal parenchyma. The patient had chronic renal insufficiency because of an inadequate amount of renal tissue. This clinical case is similar to the experimental animal with three-fourths of the renal tissue removed. These animals have uremia

is clear that
In true renal
with blood
rombosis or

embolism of the renal arteries causes hypertension (Prinzmetal, Hiatt and Trigerman). One such case came under our observation. Yule thinks that occlusion of the main renal artery is an occasional cause of hypertension but that this etiology has been overstressed. The mechanism seems to be interference with the renal circulation as in the Goldblatt experiment.

(7) *Occlusion of the Renal Veins.* In a clinical case which came under my observation the patient developed thrombosis of the inferior vena cava involving both renal veins and died of uremia. His blood pressure which had previously been normal became markedly elevated with the onset of uremia (page 329). Pederson and I (1930) produced hypertension in a rabbit by constricting one renal vein and enclosing the kidney in a membrane to prevent the development of collateral circulation. There was produced a marked passive congestion of the kidney with slowing of the renal blood flow. The membrane caused a marked fibrous thickening of the capsule of the kidney which further compressed the renal parenchyma. The blood pressure rose gradually and remained at a high level for about two months, after which it began to decrease. Page's method of producing experimental hypertension is the same as ours except that he did not constrict the renal vein.

(8) *Periarteritis Nodosa.*—Many cases of periarteritis nodosa are associated with hypertension and in such instances there are usually numerous thromboses in small renal arteries with multiple

small infarcts Presumably this type of hypertension is due to interference with the renal circulation (*See* page 331)

(9) *Renal Tumors* —Horton in a study of 355 nephrectomies for hypernephroma found no consistent fall of blood pressure after removal of the tumor Other reports are in agreement with Horton However Koons and Ruch reported a case of hypertension in a child with a Wilms tumor in which the blood pressure returned to normal after nephrectomy Pincoffs and Bradley described 4 similar cases No satisfactory explanation of this hypertension has been proposed (*See* page 439)

(10) *Pyelonephritis* —Several papers have been published in which it was maintained that bilateral chronic pyelonephritis usually caused hypertension but in some of these publications cases of glomerulonephritis and malignant hypertension have been included In our autopsies 7 of 22 cases of chronic bilateral pyelonephritis had hypertension Two of these had chronic glomerulnephritis another had terminal acute thromboarteritis of the renal [illegible]

the blood pressure in 180 cases of chronic bilateral pyelonephritis They found hypertension (145/90 mm Hg) in 9 1 per cent of controls and 16 8 per [illegible]
years of age [illegible]
was 37 9 per [illegible]
pyelonephritis This suggests that pyelonephritis sometimes causes [illegible]

glomerulonephritis or a primary hypertension (page 306)

Some patients with unilateral pyelonephritis have hypertension and in a few of these cases the blood pressure has remained normal for one year or more after the nephrectomy In the majority of cases nephrectomy does not relieve the hypertension The cases which respond favorably are probably not examples of primary hypertension It is difficult to understand how unilateral pyelonephritis can cause hypertension when the bilateral form of the disease so seldom does so (*See* page 310)

(11) *Narrowing of the Small Renal Arteries and Arterioles* — Hypertension is almost invariably present when the small renal arteries and arterioles are markedly narrowed from disease The blood pressure is especially high in "malignant" hypertension in which these vessels are almost completely closed One may believe that the vascular lesions are intensified by hypertension but there can be no doubt that extreme narrowing of the renal vessels causes

hypertension This topic will be discussed further in a subsequent paragraph

(12) *Eclampsia* —There is some doubt as to whether eclampsia should be included under renal diseases since we are by no means certain that the hypertension is of renal origin A large proportion of eclamptics show at autopsy a definite narrowing of the glomerular capillaries (page 254) The glomerular lesions must interfere with the renal circulation and may be the cause of the hypertension In most cases renal blood flow remains within normal limits but the filtration fraction is reduced and there is oliguria with a normal specific gravity (Wellen Welsh and Taylor Chesley)

(13) *Tubular Diseases* —Hypertension develops frequently in the course of severe tubular injury although it is absent in the majority

The anatomical features of a renal disease which appear to be responsible for hypertension are widespread obstruction of the glomerular capillaries (glomerulonephritis) severe obstruction of the small arteries and arterioles (malignant hypertension) or occlusion of the main renal artery or vein Hypertension nearly always develops when there is an obstructive disease of the vascular system of the kidney [illegible]
nephritis are not vasc [illegible]
tension even in the st [illegible]
vascular disease but the large cysts frequently compress the blood vessels

Decreased renal blood flow cannot be the responsible influence since the renal blood flow is decreased not only in renal diseases that cause hypertension but also in pyelonephritis and hydronephrosis which seldom cause hypertension

Ischemia of the persistent parenchyma has however not been [illegible] sels are not [illegible] lood to the [illegible] s there is a [illegible] ow whether there is ischemia of the tubules which still function

In summary practically all renal diseases in which there is severe obstruction of the capillaries arteries or veins produce hypertension while the non vascular renal diseases seldom do so Reduction in the total renal blood flow does not seem to be responsible for hypertension since it occurs in non hypertensive renal diseases but ischemia of the functioning parenchyma has not been excluded

There is a parallelism between hypertension secondary to renal disease and the experimental hypertension produced by Goldblatt since both are characterized by interference with the renal circulation but we have no direct evidence at this time that the diseased human kidney produces a pressor substance

Experimental Renal Hypertension. Bell and Pedersen produced

hypertension in one rabbit by constricting the renal vein and wrapping the kidney in a membrane to prevent the development of a collateral circulation Page wrapped both kidneys in cellophane capsules and obtained hypertension without constriction of the renal vessels The capsule about the kidney causes a great increase of fibrous tissue which compresses the renal parenchyma (Fig 99) Recently Farrell and Young reported a case of hyper tension in a boy eighteen years old due to compression of one kidney by a hemorrhagic cyst After nephrectomy the blood pressure returned to normal

A simpler method [illegible] was devised by G[illegible] to the renal art[illegible] degree of constriction When only one artery is clamped hyper tension develops but does not persist permanently but clamping of both arteries produces a permanent hypertension



Fig 99 —Experimental hyperten on produced by a capsule around the kidney and constr ct on of the renal ve n (Bell and Pederse) Note the th ck fibrous capsule about the small k dney Normal k dney on the r ght Photograph

Grollman produced chronic hypertension by wrapping a tape firmly about the poles and body of the kidney Both kidneys are taped when it is desired to produce hypertension rapidly This procedure is simpler than Goldblatt s method

Rau sprayed the surface of the kidney with a plastic which upon hardening compressed the parenchyma When this is done bilat

tension when the circulation is restored

All of the experimental procedures described above interfere with the blood supply of one or both kidneys and it appears that this

disturbance is in some way responsible for the hypertension. It was demonstrated by several investigators that denervation of the kidneys has no effect on experimental renal hypertension and it was then inferred that a pressor substance is elaborated in the renal tissue (Freeman and Page).

Goldblatt and others believe that constriction of the renal arteries reduces the renal blood flow and that renal ischemia causes the formation of a pressor substance in the kidneys which is then liberated into the blood stream. Goldblatt believes that renal ischemia is the primary cause of nearly all forms of clinical hypertension, including primary hypertension and the hypertension associated with coarctation of the aorta.

Renal Ischemia in Experimental Hypertension.—Since the renal arteries are constricted the natural inference would be that renal blood flow is reduced and that renal ischemia exists, and there seems to be no doubt that this is true when the arteries are severely constricted. Levy, Light and Blalock found decreased renal blood flow and lower blood pressure distal to the constriction but several other investigators do not agree that moderate constriction of the renal artery produces a permanent decrease of renal blood flow. Enger, Linder and Sarre found that the renal blood flow returns to normal after arterial constriction yet the blood pressure rises. Schroeder and Steele also found only a transitory decrease of renal blood flow. Corcoran and Page in experiments lasting several months produced permanent hypertension with only transient decreases of the clearances of inulin and phenol red. Mason, Robinson and Blalock found that the blood pressure distal to the constriction may persist at normal levels and that it is independent of the systemic blood pressure. Friedman and associates found that renal ischemia is not necessary for the initiation or maintenance of experimental chronic renal hypertension. It has been suggested that normal renal blood flow after arterial constriction is due to dilatation of the arteries distal to the constriction. Later on the rise of systemic arterial pressure would tend to increase the flow of blood. The accumulated evidence indicates that a moderate arterial constriction may produce hypertension without causing renal ischemia and therefore that the liberation of the pressor substance is not due to renal ischemia.

The Structure of the Kidneys in Experimental Hypertension.—After moderate arterial constriction sufficient to cause permanent hypertension there may be no structural change in the kidneys or one may find a slight tubular atrophy. After unilateral severe constriction a definite diffuse tubular atrophy develops which may proceed until the tubules appear as solid cords. After bilateral arterial constriction the animal dies before severe atrophy can develop.

In dogs with experimental hypertension of the Goldblatt type the hypertension disappears after the kidney becomes markedly

atrophic (page 311 Fig 75) It appears that kidneys that have *undergone marked atrophy cease* to produce a pressor substance or that the pressor substance is neutralized by the normal kidney

structures secrete renin

Van Slyke and associates found that the renal blood flow in dogs was much greater on a high than on a low protein diet and as far as known there are no corresponding changes in blood pressure but it may be contended that even on a low protein diet there is no true renal ischemia

How does constriction of the renal artery, obstruction of the vein or compression of the kidney produce pressor effects? It is *clearly not the reduction of renal tissue that is responsible* since surgical reduction of the renal parenchyma does not cause hypertension There must be some interference with the circulation through functioning renal tissue Goldblatt and others believe that reduced blood flow to the parenchyma (renal ischemia) causes the formation and liberation of a pressor substance, probably renin but there is satisfactory evidence that renal ischemia is not necessary for the release of the pressor influence Page suggests that decreased pulse pressure may be the responsible factor, yet there is no explanation as to how this disturbs tubular function and there is increased pulse pressure in primary hypertension It is evidently not due to decreased oxygen content of the blood since severe anemias do not cause hypertension The weakening influence

interference with the renal circulation causes the release of some pressor influence but we do not know how this is brought about

Renal Ischemia in Clinical Renal Disease —As noted above all renal diseases associated with *hypertension have anatomical* evidence of decreased renal blood flow and ischemia of the persisting parenchyma but certain non hypertensive lesions e.g. pyelonephritis and hydronephrosis also show a decreased renal *blood flow* The non hypertensive lesions may possibly not have ischemia of the persisting parenchyma

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Renal Ischemia in Primary Hypertension —The proponents of the theory that primary hypertension is caused by renal ischemia

must prove (1) that there is a decreased renal blood flow, (2) that there is ischemia of the persistent renal parenchyma, and (3) that these disturbances are caused by organic changes in the renal blood vessels. It is necessary to show that the changes in the renal vessels that reduce blood flow are organic and not spastic since obviously renal ischemia cannot be both the cause and the effect of spastic changes.

(1) *Renal Blood Flow.* Renal blood flow decreases with increasing age independently of hypertension. Goldring and associates, using the diodrast clearance, found an average effective renal blood flow of 1300 cc. per minute in 16 men seventeen to thirty two years old and an average flow of 1072 cc. (about 20 per cent less) for 21 men thirty three to sixty-eight years old. By perfusion of human kidneys obtained at postmortem, Cox and Dock found the possible renal blood flow 24 per cent less in older individuals than in young adults. They also found that most kidneys from patients with hypertension without uremia have vascular beds in the normal range, but a few show great decreases in capacity for blood flow.

Friedman and associates measured renal blood flow by the diodrast clearance and glomerular filtration by the inulin clearance in patients with hypertension. They found no notable diminution of the inulin clearance. The diodrast clearance was moderately reduced in the majority but not in all. There was no marked reduction of the renal blood flow except in malignant hypertension. Chesley found a moderate reduction of renal blood flow in most cases of hypertension. Goldring, Chasis, Ranges and Smith (1941) studied the renal blood flow in 60 individuals with primary hypertension. They found the renal blood flow (diodrast clearance, C_D) below the mean normal in all but 3 cases. The inulin clearance tended to remain in the lower range of normal values until the diodrast clearance was markedly reduced. They attributed the high inulin clearance in the presence of a decreased plasma flow to constriction of the efferent arterioles which raises the intracapillary pressure in the glomeruli and increases the percentage of plasma that is filtered, the filtration fraction.

It seems well established that renal blood flow decreases with age independently of hypertension and that there is a moderate reduction in most cases of primary hypertension. In some instances there is little or no decrease of blood flow, but in the presence of renal insufficiency it is greatly reduced.

(2) *Ischemia of the Functioning Parenchyma.* Goldring and associates found the diodrast clearance (C_D) below the mean normal in all but 1 of 60 persons with hypertension. The maximum diodrast excretion (Tm_D) ranged from slightly below normal to very low. The ratio C_D/Tm_D, which measures the blood flow to the functioning parenchyma, was below normal in 43 of the 60 cases.

There was therefore some anemia of the functioning parenchyma in three-fourths of the cases

(3) *Is the Reduced Renal Blood Flow Which is Commonly Present in Hypertension Due to Organic or to Spastic Narrowing of the Renal Arterioles?*—The autopsy studies which I have made [illegible]

there is some narrowing of these vessels which might reduce renal blood flow to some extent but in over 20 per cent of typical clinical cases there is no structural change in the arterioles and no greater involvement of the large and small renal arteries than is found in non hypertensive controls of corresponding age In a fairly large percentage of cases of primary hypertension renal ischemia cannot be explained on an anatomical basis

Perhaps the best evidence that renal ischemia is due to spastic rather than to organic changes in the renal vessels was furnished by Goldring and his associates who showed that the renal ischemia of hypertensive subjects is reversible They induced renal hyper emia by injection of pyrogenic inulin and then found the renal blood flow in most instances as good as in normal subjects

It seems definitely established that renal ischemia is not the cause of primary hypertension but the effect of a spastic state of the renal arterioles Primary hypertension is therefore not basically a renal disease but severe vascular renal lesions may develop during the course of hypertensive disease which cause the blood pressure to rise to higher levels

(*h*) *The Small Peripheral Arteries and Arterioles*—The most important mechanism for regulating the blood pressure is the muscular tone in the small peripheral arteries and arterioles There can be no doubt that the fundamental disturbance in primary hypertension is increased peripheral resistance We can conceive of this only as a widespread narrowing of the peripheral vessels Only a slight narrowing is necessary to raise the pressure to hyper tensive levels since resistance varies inversely with the fourth power of the diameter of the vessel A reduction of 10 per cent in the diameter of the arterioles would raise the blood pressure from 120 to 180 mm Hg Changes of this order of magnitude cannot be determined by microscopic methods The contraction of arterioles resulting from the fall of blood pressure after death is much greater than this and is subject to unknown variations

Since there must be some narrowing of the peripheral vessels we may now consider whether it is of organic or spastic nature

(1) *Organic Narrowing of the Peripheral Vessels*—In a large percentage of cases of primary hypertension there is a disease of the small arteries and arterioles in the kidneys and to a lesser extent

in the pancreas spleen and liver, but in the greater portion of the periphery viz the skeletal muscles bones, skin and intestinal tract there is little or no demonstrable change in these vessels It is true that about 20 per cent of the blood flows through the kidneys but it is difficult to believe that organic obstruction of the arterioles is ever sufficiently extensive to increase peripheral resistance to any great degree

The larger arteries do not play a causative rôle in hypertension since the changes in these vessels are related to age and are nearly as severe in non hypertensive as in hypertensive subjects Extreme atherosclerosis of the extremities and the viscera is often not associated with high blood pressure

When the large renal arteries are examined at postmortem atheromatous plaques may appear to cause marked narrowing of the lumen (Blackman) but when such arteries are injected under normal intravascular tension these apparent obstructions disappear (Cox and Dock)

It is conceivable that the arterioles undergo age alterations that are not visible microscopically and that such changes make them less responsive to dilating influences

(2) *Spastic Contraction of the Peripheral Vessels* —The majority of investigators favor the view that hypertonus is due to a widespread spastic state of the peripheral vessels This theory is based largely on the absence of organic changes in the greater part of the vascular bed and the demonstration that the vessels of the extremities and abdominal viscera are still capable of relaxation

A spastic state of the peripheral vessels may be caused by increased vasomotor activity by a pressor substance in the blood or by a decreased response to physiological vasodilator influences

It is clear that the hypertonus in the kidneys is not of vasomotor origin since denervation of the kidneys does not increase the renal blood flow Likewise Wilkens showed that sympathectomy in hypertensive patients does not increase the blood flow to the calf of the leg Prinzmetal and Wilson found that sympathectomy increases the blood flow in the forearm of hypertensive subjects but to no greater degree than in normal persons Abdominal sympathectomy relaxes the arterioles of the abdominal viscera to a notable degree It appears that the tonus in some parts of the body of hypertensive subjects is at least in part of vasomotor origin but this is not true for the kidneys The absence of vasomotor influences in the kidneys had led to the view that primary hypertension is not of vasomotor origin but vasomotor influences are not so important under normal conditions in the kidney as in other organs Denervation of the normal kidney of the dog does not increase the renal blood flow (Rhoades) The striking influence of emotional disturbances and of rest on the blood pressure of hypertensive subjects suggests that the vasomotor system plays an

important and possibly even a major rôle in hypertensive disease

The view that primary hypertension is caused by a pressor substance in the blood is based largely on analogy with experimental renal hypertension in animals and clinical renal hypertension in man. The objections to this view were given above viz, the absence of renal disease in a great many hypertensive subjects, and the demonstration that the renal ischemia is due to a spastic state of the renal vessels

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Renin—In 1898 Tigerstedt and Bergmann isolated a pressor substance from renal tissue which they called renin. Page and his collaborators have made extensive studies of renin. They found that intravenous injection of renin produces a sharp rise of blood pressure which persists less than one hour; repeated injections show a diminishing response until finally no hypertension results. This phenomenon has not been completely explained. Page has also shown that renin does not have a direct pressor effect but first combines with a blood globulin (*renin activator*) to produce a substance angiotonin which does have a direct pressor effect causing increased tonus of the smooth muscle of the blood vessels. Renin has been demonstrated in the renal vein in experimental renal hypertension but has not been found elsewhere in the blood (Page). The renin content of a kidney with a constricted renal artery is greater than that of a normal kidney. Landis found no increased pressor content of renal tissue from cases of benign hypertension and chronic glomerulonephritis but some variable increase from kidneys of malignant hypertension. Pressor substances have not been satisfactorily demonstrated in the blood of patients with primary hypertension. Taquini and Braun Menéndez used a delicate method for determining renin in plasma. They were unable to detect renin in the arterial or venous plasma of 23 hypertensive subjects some of which had uremia. Renin has been demonstrated *in some acute* ... chronic form

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of normal renal tissue believed to contain an anti renin factor have been used in the treatment of primary hypertension (Page, *Grollman et al*)

If renin be the pressor substance responsible for experimental hypertension what causes its liberation from the kidney? It has been shown that renal ischemia is not a necessary condition. Page

suggests that in experimental hypertension the influence may be decreased pulse pressure but this factor can hardly apply to primary hypertension in which there is increased pulse pressure

As stated above Goldblatt believes that renal ischemia is the cause of both experimental and primary hypertension He postulates that there is always sufficient vascular renal disease in primary hypertension to cause renal ischemia But this explanation does not correspond with the anatomical findings in primary hypertension and it has been shown that renal ischemia is not a necessary condition even in experimental hypertension The fact that pyrogenic inulin increases the renal blood flow of most hypertensive subjects to normal levels is strong evidence that the increased tonus of the renal vessels is not of organic nature

Serious objections have been raised against the current view that experimental renal hypertension is due to release of a pressor substance from the kidney Removal of both kidneys from one of a pair of parabiotic rats causes hypertension in the nephrectomized animal (Grollman and Rule) (Braun Menendez and V Euler)

Bilateral nephrectomy in rats may be followed by hypertension on the second or third day (Braun Menendez and V Euler) Grollman kept bilaterally nephrectomized dogs alive as long as 11 days by the use of an artificial kidney and found that the animals regularly developed hypertension Grollman suggests that the normal kidney secretes something which prevents hypertension

Evidence that the central nervous system participates in experimental hypertension was furnished by Dock who showed that pithing of the central nervous system in rabbits with experimental renal hypertension causes the blood pressure to fall as rapidly and to as low a level as in normal controls In pithed rabbits a rise in arterial pressure is easily produced with epinephrine and the response is greater in previously hypertensive animals than in normal Renin also causes a rise of pressure in the pithed animal The humoral agent causing experimental renal hypertension increases the sensitivity of the arterial response to epinephrine

The Effect of Drugs Upon the Blood Pressure (1) *Trinitrin* produces a sharp fall of blood pressure in both man and the hypertensive dog which however lasts only a few minutes It is believed to be a peripheral vasodilator It dilates the small coronary vessels It must affect a large part of the vascular bed since the blood pressure falls but we do not know whether all parts of the body are affected (2) *Thiocyanates* are helpful in some cases of hypertension Goldring and Chasis report that thiocyanate will lower the blood pressure in one of every three patients Subjective improvement nearly always follows the lowering of the pressure They considered the treatment effective when the blood pressure was brought as low as 160/100 mm Hg They administered 5 gm daily for four

important and possibly even a major rôle in hypertensive disease

The view that primary hypertension is caused by a pressor substance in the blood is based largely on analogy with experimental renal hypertension in animals and clinical renal hypertension in man. The objections to this view were given above are the absence of renal disease in a great many hypertensive subjects and the demonstration that the renal ischemia is due to a spastic state of the renal vessels.

Since the hypertonus is spastic it must be due either to a pressor substance in the blood, an increased vasomotor activity, or an age alteration in the arterioles which makes them less responsive to vasodilating influences.

Renin.—In 1898 Tigerstedt and Bergmann isolated a pressor substance from renal tissue which they called renin. Page and his collaborators have made extensive studies of renin. They found that intravenous injection of renin produces a sharp rise of blood pressure which persists less than one hour; repeated injections show a diminishing response until finally no hypertension results. This phenomenon has not been completely explained. Page has also shown that renin does not have a direct pressor effect, but first combines with a blood globulin (renin activator) to produce a substance angiotonin which does have a direct pressor effect causing increased tonus of the smooth muscle of the blood vessels. Renin has been demonstrated in the renal vein in experimental renal hypertension but has not been found elsewhere in the blood (Page). The renin content of a kidney with a constricted renal artery is greater than that of a normal kidney. Landis found no increased pressor content of renal tissue from cases of benign hypertension and chronic glomerulonephritis, but some variable increase from kidneys of malignant hypertension. Pressor substances have not been satisfactorily demonstrated in the blood of patients with primary hypertension. Taquini and Fasciolo used a delicate method for determining renin in plasma. They were unable to detect renin in the arterial or venous plasma of 23 hypertensive subjects, some of which had uremia. Renin has been demonstrated in some acute hypertensive states in animals and man but not in any chronic form of hypertension.

The presence of normal renal tissue counteracts the pressor effect of a kidney with a disturbed circulation. Hypertension produced by constriction of one renal artery subsides after a few months unless the normal kidney be removed. On this principle extracts of normal renal tissue believed to contain an anti-renin factor have been used in the treatment of primary hypertension (Page, Grollman *et al.*).

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that thiocyanates have no beneficial effect on dogs with experimental hypertension (3) *Choline* Engle and Binger administered acetyl-beta-methylcholine in subcutaneous doses of 2 5 mg In normal individuals there was only a slight fall of pressure but in hypertensives a striking decrease of pressure was often observed In both hypertensive and normal dogs a marked fall of pressure occurred The authors believe that there is a deficiency of acetyl choline in hypertensive individuals Goldblatt states that the daily administration of acetyl choline did not produce a persistent lowering of the blood pressure in dogs with experimental hypertension

Many other drugs have been used by various investigators without encouraging results At present there is no satisfactory drug treatment for hypertension, but thiocyanates are worth a trial The action of the preparations described above indicates that the peripheral vessels are still capable of dilating and further experimentation should be encouraged

Is Hypertension a Compensatory Phenomenon?—Hypertension is often regarded as a compensatory adjustment to deliver the required amount of blood to the tissues against the increased peripheral resistance It would seem that with increased peripheral resistance a higher pressure is necessary if the tissues are to receive as much blood as they do under normal circumstances The heart evidently accomplishes its increased task since the cardiac output per minute is not decreased, but we do not know whether the same proportionate amount of blood goes to each organ after hypertension is established From the clinical standpoint there is usually a rough parallelism in the individual patient between the intensity of his symptoms and the height of his blood pressure There are some exceptions but the majority of patients feel better when their pressure is reduced to moderate hypertensive levels When the pressure is reduced to normal levels many patients are less comfortable than with a moderate hypertension The lowering of the blood pressure seems to have no effect on renal function Georgopoulos found no change of urine flow under marked variations of pressure in the same individual Page lowered the blood pressure of hypertensive persons in various ways but found no difference in urea clearance between high and low levels of blood pressure It appears that hypertension is not compensatory in the sense of improving renal function Very high pressure tends to cause head-

tensive levels, but is often inadvisable to try to keep it at normal

levels There is no evidence that the increased blood pressure improved the function of any organ

studies show a preponderance in certain families of apoplexy coronary disease and hypertensive heart failure Every experienced clinician knows that when he finds a patient with hypertensive

about 90 per cent In the study of the etiology of hypertension this marked hereditary tendency must be taken into consideration

Prognosis —Blackford followed 202 patients with a systolic pressure of 175 mm Hg or higher and a diastolic pressure of 100 mm Hg or more for eight years About two thirds of the patients were females The mortality at the end of eight years was 42 per cent for the females and 70 per cent for the males Thirty nine of the surviving females were relatively free of symptoms but of 13 surviving males only 3 were symptom free Hubener cites numerous instances of survival for ten years or longer with a blood pressure of 200 mm Hg or higher A few such cases have come under my observation When the pressure is consistently below 160 mm Hg life expectation is not greatly shortened

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DIABETES MELLITUS

The incidence of diabetes in the autopsies at the University of Minnesota is shown in Table 63 It will be noted that diabetes is more than twice as frequent in females as in males This is in accord with the majority of statistical reports The maximum incidence is in the seventh decade and about 88 per cent of the cases were in persons over forty years of age

The various causes of death in diabetics are listed in Table 64

Coma is the most frequent cause of death in young diabetics but is

cases of diabetes at the Mayo Clinic found no clear evidence that diabetes promotes hypertension Hypertension (150 90 mm Hg or higher) occurred in 16 2 per cent of males and 26 7 per cent of females John 1932 found that 54 3 per cent of diabetics had a

TABLE 63 — DISTRIBUTION OF DIABETES WITH RESPECT TO AGE AND SEX

	Males			Females		
		Diabetics			Diabetics	
Age years	No of Autopsies	No	%	No of Autopsies	No	%
0–10	4409	7	0 16	3205	2	0 6
10–20	951	9	0 95	820	14	1 7
20–30	1843	13	0 7	1627	28	1 6
30–40	2872	37	1 3	1899	36	1 9
40–50	4565	46	1 0	2247	51	2 3
50–60	6099	116	1 9	2660	134	5 0
60–70	6225	188	3 0	2791	199	7 1
70–80	4624	115	2 5	2416	129	5 3
80–100	1085	33	2 0	984	33	3 4
Total	33 273	564		16 649	626	
40 yrs +	23 198	498	2 1	11 098	546	4 9

TABLE 64 — CAUSES OF DEATH IN DIABETES

Age years	Number of cases	Coma	Staphylococcic infections	Other pyogenic infections	Tuberculosis	Coronary disease	Gangrene	Encephalomalacia	Cerebral hemorrhage	Myocardial failure	Uremia	Hypoglycemia	Non infectious diseases
0–30	73	58 9	6 8	11 0	6 8	0	0	0	0	1 4	2 7	1 4	11 0
30–50	170	33 5	11 8	10 0	7 6	10 0	2 9	2 4	2 1	1 2	5 9	3 5	9 4
50 100	953	8 5	7 9	7 7	2 6	18 9	15 4	5 2	1 9	6 0	2 6	0 5	22 7

systolic pressure between 100 and 140 mm Hg Hypertension (150 mm Hg or higher) was found in 36 per cent of males and 54 per cent of females over fifty years of age

The incidence of hypertension in diabetes cannot be determined accurately from our postmortem records since a great many patients were admitted in diabetic coma or in shock from coronary thrombosis In the group free of these complications hypertension is somewhat more frequent than in non-diabetics of corresponding age

TABLE 65 — INTIMAL DISEASE OF THE SMALL RENAL ARTERIES IN DIABETICS WITH RESPECT TO AGE

		Degree of involvement per cent			
Age years	No of Cases	0	1	2	3
0–10	9	100	0	0	0
10–20	22	91 0	9 0	0	0
20–30	32	68 7	21 9	3 2	6 2
30–40	57	49 1	31 6	3 5	15 8
40–50	84	15 5	38 1	21 4	24 9
50–60	214	0 9	27 6	40 2	31 3
60–70	331	0 3	15 4	37 8	46 5
70–80	216	0 0	9 7	33 3	56 9
80–100	60	0 0	6 7	23 3	70 0
50 years +	821	0 3	16 4	36 1	47 1
Controls 50 years +	311	0 0	37 3	32 1	30 5

Intimal Disease of the Small Arteries —The degree of intimal thickening in the small renal arteries of diabetics is shown in Table 65 Intimal disease is definitely more severe in diabetics than in the non-diabetic, normotensive controls, but this may not be due entirely to the diabetes since the majority of the older diabetics had hypertension But diabetes must play an important role in accelerating atherosclerosis since coronary disease is much more frequent in diabetics than in non-diabetics (Clawson and Bell) Likewise gangrene of the lower extremities is many times more frequent in diabetics

TABLE 66 INCIDENCE AND DEGREE OF RENAL ARTERIOLOSCLEROSIS IN DIABETES WITH RESPECT TO AGE

Age years	No of Cases	Degree of involvement per cent 0	1	2	3	Total 1 to 3
1 10	9	100	0	0	0	0
10–20	22	100	0	0	0	0
20–30	31	71 0	12 9	3 2	12 9	29 0
30–40	57	70 1	8 8	0 0	21 0	29 8
40–50	84	46 4	22 6	6 0	25 0	53 6
50–60	214	36 4	19 6	15 0	28 9	63 5
60–70	331	26 6	19 6	17 2	36 3	73 1
70–80	216	25 0	23 1	18 0	33 8	75 0
80–100	60	25 0	28 3	8 3	38 3	75 0
50 years +	821	28 6	21 3	16 2	33 9	71 4
Controls 50 years +	312	83 6	13 4	2 6	0 3	16 3

Renal Arteriolosclerosis in Diabetics —In Table 66 the frequency of renal arteriolosclerosis in the various decades is shown Arteriolosclerosis appears in the third decade and is present in 71 4 per cent of those over 50 years of age Hypertension is no doubt a factor but the renal arterioles are frequently affected in normotensive diabetics

Renal arteriolosclerosis is definitely more severe in diabetic females than in diabetic males and this feature may explain the greater frequency of intercapillary glomerular lesions in females (Page 400)

The characteristic change in the arterioles is a subintimal deposit of a hyaline material The hyaline layer is thicker in diabetics than in non-diabetics with hypertension and it often replaces the greater part of the muscular layer (Figs 88 100) A thick homogeneous hyaline deposit in the arterioles is strong presumptive evidence of diabetes When the afferent arteriole is involved the efferent arteriole is usually affected to about the same degree (Fig 101) Arteriolosclerosis is more severe in those who had a blood pressure of 200 mm Hg or higher than in those with pressure at lower levels

One may believe that hypertensive diabetics are merely individuals who develop both primary hypertension and diabetes but a

TABLE 63 —DISTRIBUTION OF DIABETES WITH RESPECT TO AGE AND SEX

	Males			Females		
		Diabetics			Diabetics	
Age years	No of Autopsies	No	%	No of Autopsies	No	%
0–10	4409	7	0 16	3205	2	0 6
10–20	951	9	0 95	820	14	1 7
20–30	1843	13	0 7	1627	28	1 6
30–40	2872	37	1 3	1899	36	1 9
40–50	4565	46	1 0	2247	51	2 3
50–60	6099	116	1 9	2600	134	5 0
60–70	6225	188	3 0	2791	199	7 1
70–80	4624	115	2 5	2416	129	5 3
80–100	1685	33	2 0	984	33	3 4
Total	33 273	564		16 049	626	
40 yrs +	23 198	498	2 1	11 098	546	4 9

TABLE 64 —CAUSES OF DEATH IN DIABETES

Age years	Number of cases	Coma	Staphylococcic infections	Other pyogenic infections	Tuberculosis	Coronary disease	Gangrene	Encephalomalacia	Cerebral hemorrhage	Myocardial failure	Uremia	Hypoglycemia	Non infectious diseases
0–30	73	58 9	6 8	11 0	6 8	0	0	0	0	1 4	2 7	1 4	11 0
30–50	170	33 [illegible]	11 8	10 0	7 6	10 0	2 9	2 4	2 1	1 2	5 9	3 5	9 4
50 100	953	8 5	7 3	7 7	2 6	18 9	15 4	5 2	1 9	6 0	2 6	0 5	22 7

systolic pressure between 100 and 140 mm Hg Hypertension (150 mm Hg or higher) was found in 36 per cent of males and 54 per cent of females over fifty years of age

The incidence of hypertension in diabetes cannot be determined accurately from our postmortem records since a great many patients were admitted in diabetic coma or in shock from coronary thrombosis In the group free of these complications hypertension is somewhat more frequent than in non-diabetics of corresponding age

TABLE 65 — INTIMAL DISEASE OF THE SMALL RENAL ARTERIES IN DIABETICS WITH RESPECT TO AGE

		Degree of involvement per cent			
Age years	No of Cases	0	1	2	3
0–10	9	100	0	0	0
10–20	22	91 0	9 0	0	0
20–30	32	68 7	21 9	3 2	6 2
30–40	57	49 1	31 6	3 5	15 8
40–50	84	15 5	38 1	21 4	24 9
50–60	214	0 9	27 6	40 2	31 3
60–70	331	0 3	15 4	37 8	46 5
70–80	216	0 0	9 7	33 3	56 9
80–100	60	0 0	6 7	23 3	70 0
50 years +	821	0 3	16 4	36 1	47 1
Controls 50 years +	311	0 0	37 3	32 1	30 5

Intimal Disease of the Small Arteries —The degree of intimal thickening in the small renal arteries of diabetics is shown in Table 6[?] Intimal disease is definitely more severe in diabetics than in the non-diabetic normotensive controls but this may not be due entirely to the diabetes since the majority of the older diabetics had hypertension But diabetes must play an important role in accelerating atherosclerosis since coronary disease is much more frequent in diabetics than in non diabetics (Clawson and Bell) Likewise gangrene of the lower extremities is many times more frequent in diabetics

TABLE 60 INCIDENCE AND DEGREE OF RENAL ARTERIOLOSCLEROSIS IN DIABETES WITH RESPECT TO AGE

Age years	No of Cases	Degree of involvement per cent 0	1	2	3	Total 1 to 3
1 10	9	100	0	0	0	0
10–20	2[illegible]	100	0	0	0	0
20–30	31	71.0	12.9	3.2	12.9	[illegible]9.0
30–40	57	70.1	8.8	[illegible]0.0	1.0	29.8
40–50	84	46.4	[illegible].6	6.0	5.0	53.6
50–60	214	36.4	19.6	15.0	8.9	63.5
60–70	331	[illegible]6.6	19.6	17.2	36.3	73.1
70–80	[illegible]16	25.0	23.1	18.0	33.8	75.0
80–100	60	25.0	8.3	5.3	38.3	75.0
50 years +	821	[illegible]8.6	1[illegible].3	16.[illegible]	33.9	71.4
Controls 50 years +	312	83.6	13.4	[illegible].6	0.3	16.3

Renal Arteriolosclerosis in Diabetics In Table 60 the frequency of renal arteriolosclerosis in the various decades is shown Arteriolosclerosis appears in the third decade and is present in 71.4 per cent of those over 50 years of age Hypertension is no doubt a factor but the renal arterioles are frequently affected in normotensive diabetics

Renal arteriolosclerosis is definitely more severe in diabetic females than in diabetic males and this feature may explain the greater frequency of intercapillary glomerular lesions in females (Page 400)

The characteristic change in the arterioles is a subintimal deposit of a hyaline material The hyaline layer is thicker in diabetics than in non diabetics with hypertension and it often replaces the greater part of the muscular layer (Figs 88 100) A thick homogeneous hyaline deposit in the arterioles is strong presumptive evidence of diabetes When the afferent arteriole is involved the efferent arteriole is usually affected to about the same degree (Fig 101) Arteriolosclerosis is more severe in those who had a blood pressure of 200 mm Hg or higher than in those with pressure at lower levels

One may believe that hypertensive diabetics are merely individuals who develop both primary hypertension and diabetes but a

TABLE 63 DISTRIBUTION OF DIABETES WITH RESPECT TO AGE AND SEX

	Males			Females		
		Diabetes			Diabetes	
Age, years	No. of Autopsies	No.	%	No. of Autopsies	No.	%
0–10	4409	7	0.16	3205	2	0.6
10–20	951	9	0.95	820	14	1.7
20–30	1843	13	0.7	1627	28	1.6
30–40	2872	37	1.3	1899	36	1.9
40–50	4565	46	1.0	2247	51	2.3
50–60	6099	116	1.[illegible]	2660	134	5.0
60–70	6225	188	3.0	2[illegible]91	199	7.1
70–80	4624	115	[illegible].5	2410	1[illegible]	5.3
80–100	1685	33	2.0	984	33	3.4
Total	33,273	564		16,649	626	
40 yrs +	33,198	498	2.1	11,098	546	4.9

TABLE 64 CAUSES OF DEATH IN DIABETES

Age, years	Number of cases	Coma	Staph. locus of infection	Other pyogenic infections	Tuberculosis	Coronary disease	Gangrene	Encephalomalacia	Cerebral hemorrhage	Myocardial failure	Uremia	Hypoglycemia	Noninfectious diseases
0–30	73	58.9	6.8	11.0	6.8	0	0	0	0	1.4	2.7	1.4	11.0
30–50	170	33.[illegible]	11.8	10.0	7.6	10.0	[illegible].9	2.4	2.1	1.[illegible]	5.9	3.5	9.4
50–100	9[illegible]3	8	7.9	7.7	6	18.9	15.4	5.[illegible]	1.9	6.0	2.[illegible]	0.5	22.7

systolic pressure between 100 and 140 mm Hg. Hypertension (150 mm Hg or higher) was found in 36 per cent of males and 54 per cent of females over fifty years of age.

The incidence of hypertension in diabetes cannot be determined accurately from our postmortem records since a great many patients were admitted in diabetic coma or in shock from coronary thrombosis. In the group free of these complications hypertension is somewhat more frequent than in non-diabetics of corresponding age.

TABLE 65 INTIMAL DISEASE OF THE SMALL RENAL ARTERIES IN DIABETICS WITH RESPECT TO AGE

		Degree of Involvement, per cent			
Age, years	No. of Cases	0	1	2	3
0–10	9	100	0	0	0
10–20	[illegible]	91.0	9.0	0	0
20–30	32	68.7	21.9	3.2	6.2
30–40	57	49.1	31.6	3.5	15.8
40–50	84	15.5	38.1	21.4	24.9
50–60	214	0.9	27.6	40.2	31.3
60–70	331	0.3	15.4	37.8	46.5
70–80	216	0.0	9.[illegible]	33.3	56.9
80–100	60	0.0	6.7	[illegible]3.3	70.0
50 years +	8[illegible]1	0.3	16.4	36.1	47.1
Controls 50 years +	311	0.0	37.3	32.1	30.5

Intimal Disease of the Small Arteries—The degree of intimal thickening in the small renal arteries of diabetics is shown in Table 65. Intimal disease is definitely more severe in diabetics than in the non-diabetic normotensive controls but this may not be due entirely to the diabetes since the majority of the older diabetics had hypertension. But diabetes must play an important role in accelerating atherosclerosis since coronary disease is much more frequent in diabetics than in non-diabetics (Clawson and Bell). Likewise gangrene of the lower extremities is many times more frequent in diabetics.

TABLE 66 INCIDENCE AND DEGREE OF RENAL ARTERIOLOSCLEROSIS IN DIABETES WITH RESPECT TO AGE

Age, years	No. of Cases	Degree of involvement, per cent: 0	1	2	3	Total 1 to 3
1–10	9	100	0	0	0	0
10–20	22	100	0	0	0	0
20–30	31	71.0	12.9	3.2	12.9	29.0
30–40	57	70.1	8.8	0.0	21.0	29.8
40–50	84	46.4	22.6	6.0	25.0	53.6
50–60	214	36.4	19.6	15.0	28.9	63.5
60–70	331	26.6	19.6	17.2	36.3	73.1
70–80	216	25.0	23.1	18.0	33.8	75.0
80–100	60	25.0	28.3	8.3	38.3	75.0
50 years +	821	28.6	21.3	16.2	33.9	71.4
Controls 50 years +	312	83.6	13.4	2.6	0.3	16.3

Renal Arteriolosclerosis in Diabetes—In Table 66 the frequency of renal arteriolosclerosis in the various decades is shown. Arteriolosclerosis appears in the third decade and is present in 71.4 per cent of those over 50 years of age. Hypertension is no doubt a factor but the renal arterioles are frequently affected in normotensive diabetics.

Renal arteriolosclerosis is definitely more severe in diabetic females than in diabetic males, and this feature may explain the greater frequency of intercapillary glomerular lesions in females (Page 400).

The characteristic change in the arterioles is a subintimal deposit of a hyaline material. The hyaline layer is thicker in diabetics than in non-diabetics with hypertension and it often replaces the greater part of the muscular layer (Figs. 88, 100). A thick homogeneous hyaline deposit in the arterioles is strong presumptive evidence of diabetes. When the afferent arteriole is involved the efferent arteriole is usually affected to about the same degree (Fig. 101). Arteriolosclerosis is more severe in those who had a blood pressure of 200 mm. Hg or higher than in those with pressure at lower levels.

One may believe that hypertensive diabetics are merely individuals who develop both primary hypertension and diabetes, but a

more plausible explanation is that diabetes intensifies the hyaline *age changes in the arterioles and thus accentuates or brings about*

It was surprising to find that there is no relation between the severity of the diabetic symptoms and the degree of renal arteriolo-



Fig 100 Long tud nal sect on of an afferent arter ole in a d abet c showing grade 3 arter olosclerosis Photom crograph

sclerosis Mild diabetics whose disease was controlled by diet without insulin have as much arteriolosclerosis as those who ... re large amo nts of insulin

nerular lesions were

associated with a characteristic clinical picture, *ie* diabetes albuminuria edema and hypertension the so-called nephrotic syndrome In their experience only a small percentage of diabetics showed these glomerular lesions

Anson 1938 found 6 cases with intercapillary lesions only 2 of which showed the nephrotic syndrome Derow and associates 1939 reported one example of intercapillary lesions associated with the nephrotic syndrome



Fig 101 —Section of a glomerulus from a diabetic showing arteriolosclerosis (grade 2) in both afferent and efferent arterioles Photomicrograph

Newburger and Peters 1939 reported 4 cases with intercapillary lesions ...
noted th...
edema ...
syndrome

Siegal and Allen found the characteristic glomerular lesions in 35 of 105 diabetics over forty years of age The lesions were found in 12 of 60 diabetics without hypertension They state that there is no constant clinical syndrome associated with the lesions but

more plausible explanation is that diabetes intensifies the hyaline age changes in the arterioles and thus accentuates or brings about the hypertension From the available clinical data it appears that the diabetes precedes the hypertension in the great majority of patients From my study I am unable to distinguish hypertension due to diabetes from diabetes in a patient with primary hypertension

It was surprising to find that there is no relation between the severity of the diabetic symptoms and the degree of renal arteriolo-



FIG 100 Longitudinal section of an afferent arteriole in a diabetic showing grade 3 arteriolosclerosis Photomicrograph

sclerosis Mild diabetics whose disease was controlled by diet without insulin have as much arteriolosclerosis as those who require large amounts of insulin

lesions as a sclerosis and hyalinization of interc... tissue They also reported that these glomerular lesions were

associated with a characteristic clinical picture, viz., diabetes, albuminuria, edema and hypertension—the so-called nephrotic syndrome. In their experience only a small percentage of diabetics showed these glomerular lesions.

Anson (1938) found 6 cases with intercapillary lesions, only 2 of which showed the nephrotic syndrome. Derow and associates (1939) reported one example of intercapillary lesions associated with the nephrotic syndrome.



FIG. 101.—Section of a glomerulus from a diabetic showing arteriolosclerosis (grade 2) in both afferent and efferent arterioles. Photomicrograph.

Newburger and Peters (1939) reported 4 cases with intercapillary lesions. They consider the disease a distinct entity, but it is to be noted that they accept cases with only slight albuminuria or slight edema. Apparently they do not insist upon a well marked nephrotic syndrome.

Siegal and Allen found the characteristic glomerular lesions in 35 of 105 diabetics over forty years of age. The lesions were found in 12 of 60 diabetics without hypertension. They state that there is no constant clinical syndrome associated with the lesions, but

that there is a tendency to marked albuminuria and hypoproteinemia and that the findings often may be distinctive enough to warrant the diagnosis of intercapillary sclerosis In 10 cases with the lesions in an advanced stage only 3 presented a complete nephrotic syndrome

Horn and Smetana found 87 instances of intercapillary glomerulosclerosis in 550 diabetics In its advanced form the lesion was always associated with diabetes and was present in 59 1 per cent of diabetics with arteriolar nephrosclerosis Less severe degrees of glomerulosclerosis were found with equal frequency in cases of arteriolar nephrosclerosis without diabetes and were also found sometimes in glomerulonephritis These investigators do not think that the clinical signs and symptoms are specific for this lesion and they found the lesion in conditions other than diabetes

There are two types of glomerular lesions characteristic of diabetes the nodular and the diffuse The nodular type was first noted by *Kimmelstiel and Wilson* but *the diffuse type has not been* clearly described in the literature The diffuse lesion is more frequent than the nodular and may be present alone or in association with nodular lesions

The nodular lesion is of spherical shape and occupies the center of a glomerular lobule (Figs 102 103) The capillaries are crowded to the periphery of the lobule The diameter of the nodule varies from about 20 to over 100 microns A fibrillar structure may be demonstrated in the smaller *nodules but the larger ones* appear homogeneous and hyaline The basement membranes of the inner capillary walls are not recognizable apparently being fused with the central hyaline mass If one studies only the fully developed lesions the impression is gained that *they are intercapillary* formations

TABLE 67 INCIDENCE OF INTERCAPILLARY GLOMERULOSCLEROSIS WITH RESPECT TO AGE AND SEX

Decade and Sex	Number of Diabetics	Grade 1 and 2	Grade 3	Total Intercapillary lesions %
Males 0 to 20	14	0	0	0
Females 0 to 20	16	0	0	0
Males 20 to 40	37	2	8	27
Females 20 to 40	50	4	2	12
Males 40 to 60	131	18	8	19 8
Females 40 to 60	156	34	15	31 4
Males 60 to 100	280	43	12	19 6
Females 60 to 100	535	120	51	31 9

There is great variation in the size and number of nodular lesions in different kidneys There may be only a single nodule in a very

small percentage of the glomeruli (Grade 1) several nodules in one microscopic section (Grade 2) or a number of nodules in a majority of the glomeruli (Grade 3)

The frequency of intercapillary lesions in diabetes is shown in Table 67 The nodular and the diffuse lesions are combined in the table No lesions were found in individuals under the age of twenty years After the age of forty years the lesions are nearly twice as

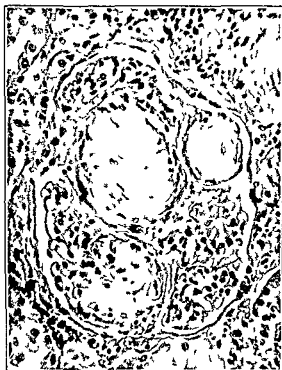


Fig 103 Diabetes mellitus Nodular hyaline lesions in a glomerulus Note that the nodules are in the centers of the lobules Photomicrograph

frequent in females which is attributable to the higher incidence of renal arteriolosclerosis in females An intercapillary lesion is merely

definitely excluded

The diabetic nodular lesions must not be confused with the central hyaline masses characteristic of chronic glomerulonephritis These are sometimes very prominent (Fig 104) The nephritic

intercapillary connective tissue In Plate IV an early diffuse lesion *is shown with beginning formation of nodular thickenings*

The "intercapillary" lesions are closely related to arteriolosclerosis In 189 cases with no arteriolosclerosis or only slight patchy hyaline deposits there were no glomerular lesions *In 131 cases with* Grade I arteriolosclerosis there was 1 with nodular lesions and 9 with Grade 1 diffuse lesions In 100 cases of Grade 2 arteriolosclerosis, 11 per cent had nodular lesions and 15 per cent had diffuse lesions

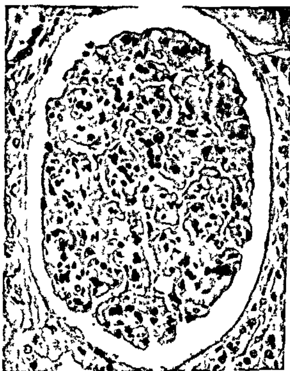


FIG 105 —Glomerulus from a case of diabetes showing the diffuse type of inter *capillary lesion Photomicrograph*

However in 148 cases of Grade 3 arteriolosclerosis 42 7 per cent had nodular and 25 per cent had diffuse glomerular lesions The arteriolar disease in some way brings about the "intercapillary" ... (Grade 3) did not produce

... e histological

diagnosis of diabetes, especially in cases which show no characteristic changes in the islands of Langerhans Nodular lesions are easily recognized They are rare in young diabetics but are found frequently in persons over 40 years of age The mild diffuse *lesions*





are not so readily identified but when they are correctly interpreted the number of positive diagnoses is greatly increased.

Edema.—Over three fourths of diabetics show no edema at any time and only 5 to 10 per cent show severe edema. Edema appears to be due to low plasma proteins and cardiac failure. When a diabetic develops uremia one may confidently predict that it is due to severe renal arteriolosclerosis with intercapillary glomerular lesions. This renal lesion will be found even though edema is not present. Hypertension with renal insufficiency in a diabetic justifies a diagnosis of intercapillary glomerulosclerosis. One need not be concerned about edema in making the diagnosis.

Albuminuria.—A majority of diabetic patients show some degree of albuminuria but the cause is not clear. Those with intercapillary sclerosis show albuminuria more frequently and the amount of albumin is usually greater but 50 per cent of those with normal glomeruli show from + to ++++ albuminuria. The presence of heavy albuminuria alone does not justify a diagnosis of intercapillary sclerosis and absence of albuminuria does not exclude this diagnosis.

Uremia.—The frequency of uremia in diabetes is shown in Table 64. It is more common in young than in elderly diabetics. The usual cause is renal arteriolosclerosis but a few patients die of uremia following an attack of diabetic coma. Following a period of coma most of the patients return to their previous state but a few develop anuria and die of uremia. No satisfactory anatomical explanation of the uremia is found in the kidneys. Dehydration is not a satisfactory explanation. It is possible that the tubules are injured by the acidosis or by a long period of low blood pressure.

Intercapillary Lesions as a Clinical Entity.—As noted above Kimmelstiel and Wilson and others regard intercapillary disease as a clinical entity characterized by diabetes, albuminuria, edema and hypertension. Siegal and Allen however found no constant clinical syndrome associated with the glomerular lesions but stated that the symptoms may occasionally be distinctive enough to warrant the diagnosis. In our experience the presence of hypertension and uremia in a diabetic usually justifies a diagnosis of intercapillary glomerulosclerosis. Edema is not an essential feature and when present it may be explained on the basis of low plasma proteins or cardiac failure.

Necrosis of the Renal Papillae.—In cases of acute pyelonephritis with formation of abscesses in the cortices there are sometimes abscesses in the medullary pyramids which cause complete necrosis of one or more renal papillae. The necrotic papillae may slough off. This lesion is associated with acute suppurative pyelonephritis and is much more frequent in diabetics than in nondiabetics because of the great frequency of renal abscess in diabetics. Microscopically the lesion resembles an infarct but contains masses of bacteria and some purulent exudate (Fig 106).

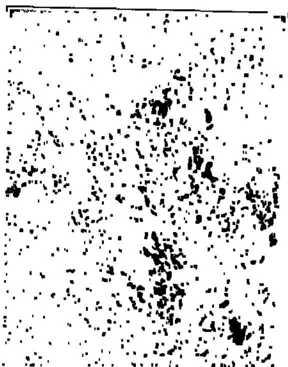


Fig 106 —Diabetes mellitus Necrosis of renal papilla The black masses are colonies of bacteria Photomicrograph Low magnification

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CHAPTER X

DISEASES OF THE KIDNEYS RELATED TO METABOLIC DISORDERS

A DISTURBANCES IN CALCIUM METABOLISM

1 **Hypervitaminosis D** —Animals injected repeatedly with preparations containing large amounts of vitamin D develop a generalized decalcification of the bones The blood calcium rises to high levels and calcium phosphate is deposited in the tubules and interstitial tissues of the kidney (Gough) Urinary calculi may be formed The reaction about the calcium deposits leads to destruction of portions of the renal parenchyma which finally results in
ard reported
iven massive
Afterwards

2 **The Effect of Hyperparathyroidism on the Kidneys** —Repeated injections of parathormone in animals cause a rise of blood calcium and decalcification of the bones Similarly parathyroid adenomas in man cause the blood calcium to rise to high levels and since the calcium is derived largely from the bones the bony tissues become decalcified and cystic The high blood calcium is accompanied by an increased excretion of calcium which takes place through the kidneys chiefly and not largely through the colon as it does normally The renal disturbances in hyperparathyroidism are attributable almost entirely to the increased excretion of calcium The polyuria and thirst which a majority of patients exhibit are probably due to increased osmotic pressure of the glomerular filtrate resulting from an increased content of crystalloids In diabetes mellitus the polyuria is attributed to the high content of sugar in the glomerular filtrate

urine with calcium salts The calculi tend to cause hydronephrosis

(Anderson Elsom Wood and Ravdin) Often there is a moderate impairment of renal function but severe renal insufficiency is rare Cases with definite renal insufficiency and hypertension have been



FIG 106 —Diabetes mellitus Necrosis of renal papilla The black masses are colonies of bacteria Photomicrograph Low magnification

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CHAPTER X

DISEASES OF THE KIDNEYS RELATED TO METABOLIC DISORDERS

A. DISTURBANCES IN CALCIUM METABOLISM

1. **Hypervitaminosis D.**—Animals injected repeatedly with preparations containing large amounts of vitamin D develop a generalized decalcification of the bones. The blood calcium rises to high levels and calcium phosphate is deposited in the tubules and interstitial tissues of the kidney (Gough). Urinary calculi may be formed. The reaction about the calcium deposits leads to destruction of portions of the renal parenchyma which finally results in some degree of renal insufficiency. Tumulty and Howard reported 2 cases of young men with fractures who had been given massive doses of irradiated ergosterol to promote bone healing. Afterwards the kidneys were unable to form a concentrated urine.

2. **The Effect of Hyperparathyroidism on the Kidneys.**—Repeated injections of parathormone in animals cause a rise of blood calcium and decalcification of the bones. Similarly parathyroid adenomas in man cause the blood calcium to rise to high levels and since the calcium is derived largely from the bones the bony tissues become decalcified and cystic. The high blood calcium is accompanied by an increased excretion of calcium which takes place through the kidneys chiefly and not largely through the colon as it does normally. The renal disturbances in hyperparathyroidism are attributable almost entirely to the increased excretion of calcium. The polyuria and thirst which a majority of patients exhibit are probably due to increased osmotic pressure of the glomerular filtrate resulting from an increased content of crystalloids. In diabetes mellitus the polyuria is attributed to the high content of sugar in the glomerular filtrate.

The increased output of calcium in the urine leads to disturbances in the kidneys of two types:

(a) *Renal Calculi.*—There is a high incidence of renal calculi in hyperparathyroidism which is attributable to oversaturation of the urine with calcium salts. The calculi tend to cause hydronephrosis and pyelonephritis (see page 418).

(b) *Deposits of Calcium in the Renal Parenchyma.*—In some cases of hyperparathyroidism there is a sufficient accumulation of calcium in the kidneys to be demonstrable in roentgenograms (Anderson, Elsom, Wood and Ravdin). Often there is a moderate impairment of renal function but severe renal insufficiency is rare. Cases with definite renal insufficiency and hypertension have been

reported by Albright and Baker and Howard but in Bellin and Gerschwin s patient there was severe renal insufficiency without hypertension In most reports it is stated that the renal function did not improve after removal of the adenoma

Autopsy reports indicate that renal insufficiency is due to obstruction of the collecting tubules by calcium casts but Anderson favors the view *that the calcification is chiefly in the interstitial connective* tissue of the medulla

The following case was studied by Dr George Fahr at the Minneapolis General Hospital A woman aged forty-eight years first developed symptoms in 1933 at the age of thirty six years She complained of nervousness confusion and inability to think She finally became unable to do any regular work In July 1940 her blood pressure was 148/104 mm Hg Because of her mental dis

ext

as

re-

arms The *blood pressure was* 140/92 *mm Hg Blood calcium* was 16 6 mg and phosphorus 6 8 mg per cent The blood urea

moglobin 66 per cent Roent

rosa cystica and a biopsy of

A small tumor in the region of the thyroid was palpated and upon removal it was found to be a parathyroid adenoma weighing 3 gm It was composed of chief cells and large vesicular cells

Following the operation the blood calcium dropped to 7 3 mg and tetany developed The tetany was controlled by parathormone and calcium The phosphorus remained high 5 4 mg per cent

On May 11 1943 *x* ray studies showed a marked improvement in the appearance of the bones but the patient stated that she had had nocturia and excessive thirst for the past year and for the past three weeks nausea vomiting and cramps in her arms and legs *She had been taking an unknown amount of calcium* and vitamin D

On August 22 1945 the patient was found to be emaciated The blood pressure was 90/70 mm Hg The blood calcium was 6 4 and the phosphorus 10 2 mg per cent *The blood urea nitrogen*

Death August 28 1945

t kidney 90 gm

and the cortices

Microscopic examination of the kidneys reveals numerous small masses of calcium nearly all of which are located in the medulla Near the apex of the medulla there are large masses of calcium collected in cystic spaces which appear to be dilated collecting tubules Numerous masses of calcium deeper in the pyramids have the shape and direction of collecting tubules (Fig 107) In the

part of the tubules occupied by the cast all the epithelial cells are either absent or calcified The calcium is in the tubules not in the interstitial tissues The fact that other substances eg urates sulfa compounds and hematin are known to be precipitated in the collecting tubules favors the view that this is the same process If the lesion is necrosis and calcification of the tubules why is it restricted almost entirely to the medulla* The dilated tubules are also evidence of obstruction by casts There remains however the problem of the

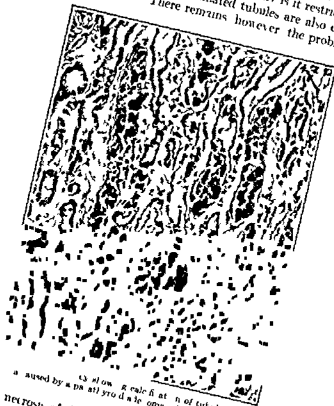


Fig 107 ... caused by a parathyroid adenoma ... showing calcification of tubules From a case of ... Photomicrograph

cause of the necrosis of the epithelial cells at the site of the casts Obstruction of tubules by casts of other types does not cause necrosis of the epithelium

In this case a large proportion of the nephrons are obstructed and a great many of the obstructed nephrons have become atrophic This is clearly the cause of the uremia

It will be noted in this case that the blood phosphate level is much higher than is usually found in hyperparathyroidism This may be explained by the renal insufficiency The kidneys have

the same difficulty in excreting phosphates as they have with urea hence the phosphates accumulate in the blood

3 **Chronic Renal Insufficiency** —*In chronic renal insufficiency* the kidneys have the same difficulty in excreting phosphate as they have with urea and the blood phosphorus often increases to high levels—10 to 20 mg per cent In the blood the phosphate tends to combine with calcium and is then excreted into the intestine as calcium phosphate Calcium is then withdrawn from the bones to maintain the normal blood level In chronic renal insufficiency there is usually but not always a decrease of calcium and an increase of phosphorus in the blood

The low blood calcium causes hyperplasia of the parathyroids In long standing chronic renal insufficiency such as occurs in polycystic renal disease it is not uncommon to find a marked enlargement of all four parathyroids The hypertrophy of the parathyroids is believed to be a result of the loss of calcium and not the primary cause Ginzler and Jaffe believe that the insufficient kidney is unable to form ammonia in sufficient amounts and base *is therefore withdrawn from the bones They attribute the rarefaction* of the bones to acidosis and not to excess of parathormone

Renal Dwarfs Chronic renal insufficiency of severe degree in *children causes stunting of skeletal growth The degree of dwarfism* depends upon the age of onset and the intensity of the renal insufficiency Dwarfism may develop in any anatomical type of renal disease It is not clear from the literature which forms of renal disease are most frequent but it is known that many renal [illegible] some [illegible] and [illegible]

The outstanding symptoms are stunted growth polyuria polydipsia and weakness Hypertension is often noted The urine is of low specific gravity and the kidneys are unable to form a concentrated urine There is usually only slight or moderate albuminuria All functional tests indicate impairment of renal function

Blood urea and non protein nitrogen are greatly increased *Blood phosphorus is usually high and blood calcium is relatively low with respect to the phosphorus*

The bones show marked rarefaction and numerous deformities such as genu valgum develop because of the weakness of the bones Some patients exhibit the bony alterations characteristic of rickets and are called renal rickets but in most instances the changes are unlike those of rickets

Death occurs usually in the second decade At autopsy one finds the bony changes mentioned above and some form of severe chronic renal disease The parathyroid bodies are usually enlarged

The sequence of events is interpreted as follows There is a

primary renal disease with renal insufficiency which causes retention of phosphates Blood calcium combines with phosphate and is lost in the intestine or the acidosis causes removal of the calcium from the bones Parathyroid hyperplasia results from the lowered blood calcium There is insufficient calcium available for ossification of the growing bones the newly formed osteoid tissue is not calcified and bony deformities result

It will be noted that primary hyperparathyroidism is characterized by high blood calcium and low phosphorus while primary

cal factors are hyperparathyroidism multiple myeloma and chronic hyperchloremic acidosis

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B EFFECTS ON THE KIDNEYS OF DISTURBANCES IN THE METABOLISM OF URIC ACID

1 **Uric Acid Infarcts** Uric acid infarcts are not infarcts in the usual sense but deposits of urates in the medullary pyramids

the same difficulty in excreting phosphates as they have with urea hence the phosphates *accumulate in the blood*

3 **Chronic Renal Insufficiency** —In chronic renal insufficiency the kidneys have the same difficulty in excreting phosphate as they have with urea and the blood phosphorus often increases to high levels 10 to 20 mg per cent In the blood the phosphate tends to combine with calcium and is then excreted into the intestine as calcium phosphate Calcium is then withdrawn from the bones to maintain the normal blood level In chronic renal insufficiency there is usually but not always a decrease of calcium and an increase of phosphorus in the blood

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The outstanding symptoms are stunted growth polyuria polydipsia and weakness Hypertension is often noted The urine is *of low specific gravity and the kidneys are unable to form a* concentrated urine There is usually only slight or moderate albuminuria All functional tests indicate impairment of renal function

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They are irregular opaque yellowish masses composed of crystals of urates They are found chiefly in children under one week of age, but may be observed infrequently in older infants The age distribution of 67 cases in our series is as follows stillborn, 3 cases, less than one day, 5, one to seven days, 41, one to four weeks, 7, one to two months, 5, two to three months, 5, and eleven months, 1 case

In microscopic sections the lesion shows dilated collecting tubules filled with urate crystals There may be a little desquamation of the lining epithelium but there is no inflammatory reaction

In the newborn infant the blood contains an excess of uric acid which is believed to come from disintegration of the nuclei of erythroblasts Uric acid is relatively insoluble and it is precipitated in the tubules when the glomerular filtrate is concentrated into the definitive urine The precipitation in the terminal collecting tubules is evidence that concentration of the tubular urine continues in the collecting tubules

There is no evidence that uric acid infarcts cause any permanent damage to the kidneys



FIG 108 —Gout nephritis External surface of kidney Note the coarse pitting Photograph

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2 **Gout Nephritis** —It has been known for many years that there is a high incidence of hypertension in persons afflicted with gout and that some gouty individuals develop renal insufficiency Schnitker and Richter in a study of 55 cases of gout found that 17 had a significant impairment of renal function Hypertension was found in 13 of the 17 patients with renal insufficiency and in 14 of the 38 without renal insufficiency These investigators reported



FIG 109 —Gout nephritis Section of a tophus in a medullary pyramid Photomicrograph

four autopsies and concluded that gout nephritis is a vascular disease of the kidneys They did not regard the urate deposits in the k[illegible]

[illegible]

deposits in the pyramids in his case in which there was renal insufficiency

Only 2 cases of gout nephritis have come under my observation and in both of these tophi in the pyramids were the cause of renal insufficiency A brief summary of 1 case is as follows

destroyed nearly all the collecting tubules (Fig 103) In the same areas the cortical tubules shows disuse atrophy

It may be concluded that gout nephritis is sometimes an atrophy of the kidneys due to precipitation of urates in the collecting tubules and subsequent formation of tophi which destroy the pyramids In other instances renal insufficiency may be due to arteriolosclerosis It appears probable that the association of renal arteriolosclerosis and gout is accidental

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C RENAL CALCULI

Renal and ureteral calculi are considered as one disease since [illegible] Vesic-

cent of

hospital admissions These data pertain to calculi that gave some clinical sign of their presence The data from our autopsies are shown in Table 68 The incidence of calculi in persons over ten years of age is 0 97 per cent *In over one third of the cases the calculi were* very small and may be regarded as non-clinical since they had produced neither hydronephrosis nor pyelitis In 287 of the 464 cases

cases However [illegible]
clinically as nephrolithiasis A stone lodged in the ureter produces renal colic but a large staghorn calculus in the renal pelvis may not produce symptoms In a majority of the patients with symptoms of nephrolithiasis death was due to uremia or *infection of the kidneys*

or to postoperative complications following nephrectomy or removal of calculi

TABLE 68 —DISTRIBUTION OF RENAL AND URETERAL CALCULI IN AUTOPSIES WITH RESPECT TO AGE

Age years	Total autopsies	Renal and ureteral calculi Clinical	Non-clinical	Total	Percentage
0–10	8110	1	10	11	0 13
10–20	1799	7	3	10	0 55
20–30	3405	11	[illegible]	13	0 38
30–40	4800	1	9	30	0 6
40–50	7083	37	17	54	0 [illegible]
50–60	9318	70	30	100	1 0
60–70	9653	72	40	11	1 16
70–80	7509	54	46	100	1 33
80–100	875	14	18	3	1 11
Totals	46 412	286	165	45	0 9

Our statistics on the incidence of clinical calculi may be accepted as accurate but our incidence of small non clinical calculi is doubtless too low since no routine search for small stones was made In a careful study of 239 autopsies Rosenow found calculi in 5 4 per cent

Age —All observers are agreed that renal calculi are rare in children In 211 cases Randall found 1 per cent under ten years

the ages of thirty and fifty years

In our clinical group there was one case under 10 years of age a child with onset of symptoms at the age of thirty months and death from uremia at the age of six years Another child had its first symptoms at the age of six years and died of uremia at the age of ten years Clinical cases in children have been described by Dietrich Behrens Campbell and others Behrens reported a case with onset of symptoms at the age of two months The maximum incidence in our series is between the ages of fifty and seventy years but this represents the age at death not the age of onset of the disease

Sex —Many observers report a preponderance of calculi in males Randall studied 135 males and 76 females Mennicken had 675 males and 388 females and Parmenter reported 227 males and 118 females In our autopsies calculi were found in 293 males and 158 females which gives an incidence of 0 97 per cent in each sex

Position —Randall found calculi on the right side only in 88 on the left only in 103 and bilaterally in 20 cases Mennicken reported 540 on the right 438 on the left and 85 bilateral Parmenter found 164 on the right 145 on the left 8 unrecorded and 28 bilateral A combination of these three reports gives the incidence of bilateral calculi about 8 per cent Postmortem statistics give a much higher

incidence of bilateral calculi In our records there are 140 on the right 185 on the left and 139 bilateral which gives a frequency of 30 per cent of bilateral stones This discrepancy may be due in part to the more advanced stage of the disease at the time of death but it suggests that small calculi in the other kidney may be overlooked clinically



FIG 110 —Calculi in the upper half of a double kidney with resulting hydronephrosis of the upper segment Photograph

In 211 clinical observations Birdsall found 150 pelvic and 61 ureteral stones In our 464 cases calculi were found in the pelves only in 395 in pelves and ureters in 20 and in ureters only in 49 which

years

Cook s patient was living after twenty two years and Barnett s

patient lived sixty years with a staghorn calculus in one kidney In 56 of our cases there was a satisfactory clinical history with respect to the renal disease and the duration of symptoms was as follows three weeks to one year 9 one to three years 8 three to five years 6 five to ten years 13 ten to fifteen years 9 fifteen to twenty years 6 twenty to twenty five years 3 and twenty five to thirty years 2 cases Presumably the stones were present much longer than the clinical symptoms indicate

Symptoms —The characteristic symptoms are attacks of dysuria hematuria pyuria and renal colic The attacks of colic correspond with the passage of stones through the ureters The intervals between attacks vary from weeks to many years Small stones may pass through the ureters without great difficulty and it is not uncommon to find small calculi in the urine from time to time One of the patients in our group passed over 300 calculi during a period of four years

Frequently a calculus passes part of the way down the ureter and then becomes permanently lodged If not removed it causes hydronephrosis and ultimately in most instances a pyelonephritis develops in the obstructed kidney This usually leads to complete destruction of the kidney

Calculi in the pelvis that are too large to enter the ureter may produce hydronephrosis by lodging in the terminal portion of the pelvis (Fig 110) Large staghorn calculi have the shape of a mold of the pelvis the branches corresponding to the calices These

hydronephrosis or non functioning kidney may be demonstrated Plummer stated that 80 per cent of renal calculi are demonstrable by roentgen-rays Stones composed of cystine xanthine or pure uric acid may not be radiopaque

Gross Morphology of Calculi Calculi are of rounded or irregular shape They often present jagged surfaces which scratch the mucous membrane In our group of 464 cases there were 80 with a single calculus less than 1 cm in diameter and there were 134 cases with one calculus from 1 to 3 cm in diameter usually alone but sometimes associated with a few small stones There were 47 examples of staghorn calculus either single or associated with smaller stones In 135 cases the calculi were numerous and less than 1 cm in diameter and in 32 cases there was more than one rather large calculus In 23 instances there were innumerable calculi described as gravel or sand Frequently small stones were associated with large calculi

Chemical Composition Calculi are composed of uric acid urates

oxalates carbonates and phosphates Some calculi consist almost entirely of one chemical substance but the majority contain two or more of those just enumerated Oxalate stones are chiefly hard and brownish urate stones are moderately hard and dirty yellow phosphate and carbonate stones are softer and whitish (Hansen) In sterile urine the stones are usually composed of uric acid or oxalates in infected urine phosphate and carbonate stones are formed (Higgins) The nucleus of a stone may be composed of one substance and its peripheral portions of another because of changed conditions in the chemical environment during its formation Cystine calculi will be discussed separately

Effects Upon the Kidney —Calculi may injure the kidneys by obstructing the outflow of urine or by inciting infection in the pelvis Stones that lodge in the ureter or the lower part of the pelvis cause hydronephrosis A completely obstructed kidney may undergo a simple atrophy and become a fibrous shell about the *calculus* *When the stone is in the ureter the adipose tissue of the* renal sinus may increase as the cortex atrophies producing the condition called lipomatosis (page 421) When the hydronephrosis becomes infected a chronic pyelonephritis may result and rarely a pyonephrosis develops Hydronephrotic kidneys become infected readily (page 297) When the calculus does not cause obstruction it may persist indefinitely without producing serious damage to the kidney but there is usually a chronic pyelitis associated with large calculi

Recurrence —Calculi frequently recur after surgical removal Cabot and Crabtree (1915) reported recurrence in 56 per cent Barney 1922 32 per cent Twinem 21 to 38 per cent Herbst 15 per cent Braasch and Foulds 10 7 per cent Hunner 9 5 per cent Higgins found a recurrence of 16 4 per cent prior to 1933 but with improved technique the incidence of recurrence between 1933 and 1939 was only 4 9 per cent Recurrence is attributed in most

2 to 8 per cent In our records there were 10 nephrectomies for nephrolithiasis and many operations for removal of stones from one to eighteen years before death In every instance stones recurred but this gives no information as to the frequency of recurrence

Etiology and Pathogenesis The formation of a calculus is a complex process that is imperfectly understood It seems to be dependent upon several factors acting either singly or in combination (1) There must be an organic matrix in which the crystalloids of the urine are first deposited to form the nucleus of the stone It has been widely believed that desquamated epithelium and inflammatory exudate furnish the matrix but Randall has proposed

a different explanation. He offers evidence that the first change in the development of a primary calculus is the formation of a calcium plaque in the apex of a renal papilla. The surface epithelium over the plaque subsequently becomes desquamated and the calculus forms on the surface of the plaque. After a time the calculus becomes detached from the papilla. Calcium plaques occur frequently. Rosenow found them in 22.2 per cent of 239 autopsies and Randall in 19.6 per cent of 1154 autopsies. Small calculi are occasionally found attached to these plaques. Randall observed such calculi in 5.6 per cent of 1154 autopsies. It seems well established that many calculi are formed in the way that Randall suggests but whether this applies to the majority of stones has not been determined. The fact that an occasional calculus contains true bone is evidence that its nucleus was formed within the substance of the kidney (Stuart and Kirkorian).

(2) *Supersaturation of the Urine With a Crystalloid.* The urine may become oversaturated with a crystalloid because of excessive excretion of the substance or because of conditions such as oliguria in which there may be undue concentration of the urine. Flocks made an interesting study of the relation of calcium excretion in the urine to the formation of calculi. In 11 of 12 normal controls he found the average daily excretion of calcium in the urine 100 to 150 mg on a low calcium intake and 250 to 300 mg on a high calcium intake. In the patients with calculi 23 of 35 excreted 420 mg daily on a high calcium intake and 21 of the 23 excreted more than 200 mg on a low calcium diet. There was no variation in the excretion of phosphorus. These observations suggest that individuals who excrete an undue proportion of calcium in the urine are predisposed to the formation of calculi. Lieberman produced calcium plaques on the renal papilla in 2 of 31 dogs given repeated injections of parathormone.

In hyperparathyroidism there is excessive excretion of calcium and the incidence of renal calculi is high in this disease. Cystine calculi form only in those who have cystinuria. Uric acid is ten to twenty times as soluble in urine as in water. It is held in solution in urine by a colloid mechanism which fails when an excessive amount is excreted. In gout the blood uric acid is abnormally high and uric acid is often deposited in the collecting tubules.

(3) *Infection.* Infection appears to play a role in the formation of calculi but in most instances the calculus probably precedes the infection. Rovsing in 716 cases found that 76 per cent were aseptic. In our 311 autopsy cases about 40 per cent showed gross pyelitis or pyelonephritis but no bacteriological studies were made. Higgins found infection in three-fourths of his recurrent cases. In the great majority of our infected cases there was hydronephrosis and it is known that hydronephrosis predisposes the kidney to hematogenous infection. Since calculi often traumatize the pelvic

mucosa one might expect these injured areas to become infected through the blood stream Calculi are found in only a small percentage of cases of infected hydronephrosis

In our 133 cases of renal tuberculosis there were only 3 with calculi Calculi may develop in primary renal infections as well as in kidneys invaded by malignant tumors but they do so infrequently An infected urine is believed to promote the formation of carbonate and phosphate accumulation about a calculus On the whole the evidence indicates that infection is seldom the primary cause of a calculus

(4) *Obstruction* —Obstruction of the urinary passages is believed to promote the formation of calculi Blocks found that stasis increases the calcium content of the urine but does not affect the total calcium excretion The importance of obstruction is suggested by the fact that practically all vesical calculi occur in males But too much emphasis should not be placed on obstruction since very few hydronephrotic kidneys contain calculi except when the calculus itself is the cause of the hydronephrosis

Prolonged immobilization of the body such as occurs in severe paralytic poliomyelitis or from traumatic injuries of the spinal cord may lead to the development of renal calculi but such patients often have hydronephrosis which may be a contributory factor

(5) *Vitamin Deficiency* Vitamin A deficiency is a possible factor in the formation of calculi Rats on a diet deficient in vitamin A develop renal calculi (Higgins) Higgins and Mendenhall found that 25 per cent of their patients with calculi showed vitamin A deficiency by the biophotometer test but Flocks found only 1 in 35 with vitamin A deficiency Erickson and Feldman found that 24 of 25 patients with calculi showed deficiency of

vitamin A did not improve the patients with deficiency and the authors suggested that the vitamin deficiency might be in effect rather than a cause of calculi

(6) *Hyperparathyroidism* Albright believes that hyperpara ... se of calculi but other observers find ... o 0 2 per cent (Griffin *et al* ... h incidence of renal calculi in ... because of the excessive excre- ... ajority of calculi are unilateral suggests that a local disturbance in the kidney is usually a determining influence

Cystinuria is a hereditary familial metabolic disorder which causes no symptoms unless calculi form Cystine calculi are said to occur in about 2 5 per cent of persons with cystinuria It is recommended

that patients with cystine calculi be given alkalies and kept on a vegetarian diet

Calculi that are producing damage to the kidney should be removed surgically when possible. This applies to all calculi associated with infection. Aseptic calculi need not be removed unless they are causing hydronephrosis. In the medical management of calculous disease the various etiological factors mentioned above should be investigated. It is particularly important to clear up any infection that may be present since this tends to destroy the kidney.

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LIPOMATOSIS OF THE KIDNEY

Lipomatosis of the kidney refers to the replacement of the renal area by adipose tissue Clinically the involved kidney excretes little or no dye and sometimes pus may be obtained from its ureter In the majority a stone is found in the pelvis or ureter In a retro grade pyelogram the calices are not filled On exploration or at autopsy the kidney is usually enlarged sometimes to enormous proportions and it is composed almost entirely of adipose tissue On midsagittal section one finds a thin layer of renal parenchyma surrounding a mass of adipose tissue and covered externally by a thick layer of perirenal fat (Fig 111) Upon dissection there is found a small rounded pelvis connected to the atrophic cortical *layer by long very narrow calices* *The adipose tissue is in the*

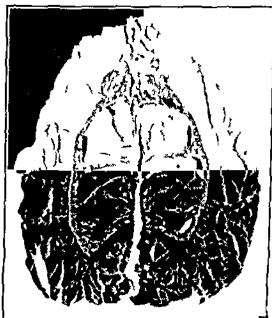


FIG 111 —Lipomatosis of the kidney due to obstruction by a calculus Note the large amount of pelvic and perirenal adipose tissue and the thin layer of cortex Photograph

sinus of the kidney surrounding the calices—it is not in the renal parenchyma

It is believed that there is a primary atrophy of the kidney without hydronephrosis caused usually by a calculus but sometimes by pyelonephritis or some other disease The fatty tissue in the sinus increases as the parenchyma shrinks An early stage *of lipomatosis is shown in* Figure 112 Kutzmann collected 33 cases *from the literature* 26 *of* which were due to calculi He thought that the fat accumulated within the renal parenchyma

Young reported 10 cases with either calculus or infection and 1 case with neither of these diseases Young showed that the fat accumulates around the calices Priestley reported a lipomatous kidney weighing 1000 gm and containing a staghorn calculus In one of our cases the kidney was enormously enlarged weighing over 1000 gm

Hamm found that lipomatous atrophy occurs in mild degree with senile atrophy when there is neither calculus nor pyelonephritis He states that it occurs only in obese individuals

The best interpretation of lipomatosis of the kidney is an atrophy of the kidney due to obstruction by a calculus pyelonephritis or

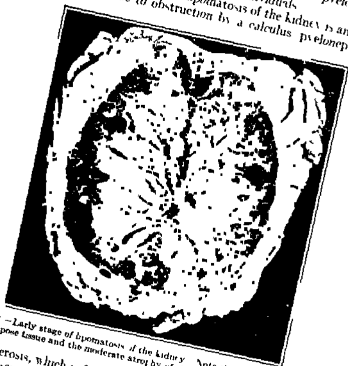


Fig 112 —Early stage of lipomatosis of the kidney Note the increase of pelvic adipose tissue and the moderate atrophy of the cortex Photograph

arteriosclerosis, which is followed by replacement lipomatosis The adipose tissue is derived from that normally present in the renal sinus The perirenal fat also increases It is not a true neoplasm but in kidneys weighing over 1000 gm the growth of the fat assumes a benign neoplastic quality

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CHAPTER XII

TUMORS OF THE KIDNEYS

A CONVENIENT classification of renal tumors is as follows

- A Connective tissue tumors
  - 1 Fibroma
    - (*a*) Cortical
    - (*b*) Medullary
  - 2 Lipoma
  - 3 Leiomyoma
  - 4 Hemangioma
  - 5 Tumors associated with tuberous sclerosis
  - 6 Sarcoma
- B Epithelial tumors
  - 1 Adenoma
    - (*a*) Papillary cystadenoma
    - (*b*) *Solid adenoma (small hypernephroma)*
  - 2 Adenocarcinoma (hypernephroma)
- C Wilms tumors
- D Tumors of the renal pelvis

A CONNECTIVE TISSUE TUMORS

1 **Fibroma** —(*a*) *Cortical Fibromas* —Small subcapsular fibromas, a few millimeters in diameter, are found occasionally at post mortem but fibromas of sufficient size to produce clinical symptoms are very rare Kukudshanoff reported a pure fibroma from a woman thirty-six years of age, which measured 12 x 8 x 6 cm Clar (1933) described a fibroma 15 x 13 x 9 cm from a male thirty years old, and collected 10 other clinical cases from the literature Eight successful nephrectomies have been recorded Large fibromas give symptoms not unlike those of carcinoma

(*b*) *Medullary Fibromas* —These tumors are situated in the medullar

ameter

areas

kidneys They produce no symptoms Microscopically (Fig 113) they are rather well circumscribed and are composed of dense fibrous tissue interspersed with areas of mucinous stroma Occasionally a renal tubule passes through the tumor The usual interpretation is that of a developmental defect (hamartoma), but Zangemeister considers them true benign neoplasms since they increase in frequency up to the age of fifty years

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Fi... graph Low magnification

2 Lipo... — This discussion is limited to intrarenal lipomas and does not include the perirenal tumors nor lipomatosis of the kidney. Small non-clinical cortical lipomas are often observed in routine autopsies, but lipomas of large size are very rare. Robertson and Hand 1941, were able to assemble only 14 clinical cases. The clinical symptoms are about the same as those produced by carcinoma, viz., pain, enlargement of the kidney, tenderness and deformity of the pelvis in the urogram. Hematuria is sometimes mentioned. The reported tumors vary from 3 cm to over 10 cm in diameter. Occasionally multiple lipomas are described. The tumors consist largely of adult adipose tissue cells but small amounts of smooth muscle, striated muscle fibrous tissue and cartilage are mentioned in some reports. Our single case of lipoma was an accidental autopsy

finding in a woman seventy six years old who died of carcinoma of the bladder The tumor was 8 cm in diameter and occupied the lower pole of the left kidney A few striated muscle fibers were interspersed among the fat cells

Liposarcoma —Seven cases have been reported in which sarcomatous areas were found in a lipoma The sarcomatous areas are composed of spindle-shaped cells exhibiting mitoses—apparently fibroblasts not yet differentiated into fat cells McCartney and Wynne s tumor was 6 cm in diameter while those reported by Hartwig and Froug were very large No metastases have been reported Froug s patient had tuberous sclerosis

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3 **Leiomyoma** —Small subcapsular leiomyomas a few milli meters in diameter may often be found in routine autopsies Apparently these small growths develop from smooth muscle in the capsule Kretschmer described a subcapsular leiomyoma 9 x 2 mm Gordon and associates collected from the literature 17 cases with symptoms which were subjected to surgical operation The ages ranged from twenty one to seventy-one years Eight of the 17 cases were diagnosed as malignant but only 2 terminated fatally One of the fatal cases was reported by Cooke who found a malignant leiomyoma with metastases to the liver and omentum Gordon s own case was a benign myoma measuring 12 x 15 x 7 cm

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4 *Hemangioma* —*Thirty-one cases of hemangioma of the kidney* were collected by Cabot in 1936 They were distributed from young adult life to old age but the great majority occurred before the age of *forty years* *The outstanding symptom is* hematuria which may be in the form of severe hemorrhages at irregular inter

ɾ ··· ɔd of years Colicky pains

the ureters

grade pyelo-

grams may show no deformity other than ··· defects due to *blood clots* but in the case of massive or multiple tumors there

may be dilatation and deformity of the calices When urograms are negative the clinical diagnosis may be essential hematuria (Webb-Johnson and Warwick) It is seldom that a correct diag
ly may become necessary

ed by the presence of a conspicuous hemangioma of the skin (Dean and McCarthy) or an angioma of the urinary bladder (Cirio)

When the kidney is opened by midsagittal section the angioma may be demonstrated It may be single multiple or diffuse McLean and Mathews described a peripelvic cavernous growth Dean and McCarthy observed a large tumor 13 x 10 x 5 cm which was partly of cavernous structure and partly solid consisting of small vessels Most of the tumors are of cavernous type No malignant angiomas have been reported

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5 **Tumors Associated With Tuberous Sclerosis** — In over ne half of the cases of tuberous sclerosis multiple bilateral benign tumors are found in the kidneys The tumors are lipomas leiomyomas fibromas angiomas epithelial growths of adenomatous structure and mixtures of these various tissues Areas of sarcomatous structure may be found but metastasizing tumors have not been reported The tumors may be so large or so numerous that renal insufficiency develops It is believed that the tumors arise from developmental defects in which the tissues replacing the renal parenchyma assume neoplastic qualities

6 **Sarcoma** —Sarcoma of the kidney is diagnosed at the present time much less frequently than formerly since it is now realized that the great majority of tumors which appear to be sarcoma on examination of a few sections prove to be undifferentiated epithelial tumors when a large number of areas are studied This is also true of thyroid tumors The renal tubules differentiate from a cellular mesenchymal tissue and the undifferential portions of epithelial tumors resemble the original mesenchyma The growing edges and the metastases of an adenocarcinoma of the cortex

oma
until

Nevertheless true sarcomas do occur In our series of renal tumors there was only one sarcoma and this was regarded as a fibrosarcoma because of the presence of numerous collagenous fibers among the tumor cells Herman and Greene reported a round cell sarcoma from a girl aged seventeen years and a lymphosarcoma from a man aged thirty eight years In a series of 130 renal tumors Soloway found 3 sarcomas In a series of 568 renal tumors Priestley found 32 sarcomas (5 per cent) It is highly probable that many of the tumors reported as sarcomas are spindle cell adenocarcinomas of the cortex

Liposarcoma has been discussed in a preceding paragraph Adenosarcoma is a type of Wilms tumor

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B EPITHELIAL TUMORS

1 **Adenoma** —Adenoma may be defined as a benign epithelial tumor but the distinction between adenoma and carcinoma is often arbitrary especially in the case of solid adenoma

(*a*) *Papillary Cystadenoma* —The vast majority of cystadenomas are small non clinical growths only a few millimeters in diameter situated at or near the surface of the renal cortex They are often multiple They occur chiefly in persons past middle life and they develop in cortical scars resulting from sclerotic closure of renal arteries In the cortical scars the glomeruli and tubules usually undergo atrophy and disappear completely but occasion

rom a
114)
cells

or it may develop papillary intracystic processes and develop to macroscopic dimensions (Fig 115) The papillary processes may become so closely packed that the growth becomes solid (Fig 116) The lining epithelium is of dark cubical type but occasional cells

attain sufficient size to produce clinical symptoms Judd 19-- described a tumor from a woman aged fifty-one years which had produced pain and hematuria for eleven years The tumor measured 13 x 11 x 5 cm and had a tubular structure Dschu Yu Bi 1934

found the right kidney greatly enlarged (18 x 8 x 7 cm) and filled with papillary cystadenomas and tubular adenomas—the largest being 8 x 7 x 5 cm The patient was a male aged thirty seven years and had a painful enlarged kidney

Proskauer, 1940, reported 2 cases

1 A woman fifty-four years old with symptoms for eight years The tumor was a papillary and tubular cystadenoma measuring 25 cm in diameter The patient was well two years after nephrectomy

2 A woman sixty-one years old with symptoms of indefinite duration The tumor was described as a papillary adenoma and weighed 1960 gm

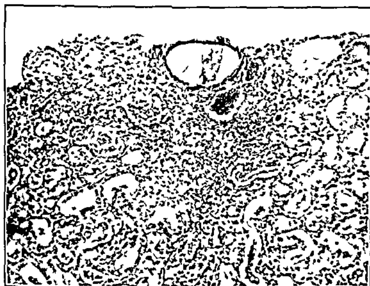


Fig 114 —Persistent tubule in a cortical scar resulting from a sclerotic artery which has formed a small cyst [illegible]

Kalk and Huckel 1940 found a tumor at postmortem in a man seventy-three years of age who had had pain and hematuria for one year The right kidney weighed 5750 gm and was almost entirely replaced by a papillary cystadenoma The tumor was regarded as the cause of death

It appears therefore that dark-cell papillary cystadenomas in rare instances may attain a massive size and produce symptoms but they do not metastasize nor assume the appearance of adenocarcinoma Cabot and Middleton however regard all adenomas as basically malignant

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FIG 115 —Papillary cystadenoma in a cortical scar Photomicrograph



FIG 116 —Papillary cystadenoma with closely packed processes Macroscopically the tumor appeared solid Photomicrograph

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(b) *Solid Adenomas* —These are small solitary cortical tumors composed of solid cords of cells with clear or dark cytoplasm and



FIG 117 —Solid adenoma composed of solid cords of dark cells Photomicrograph

a diameter of less than 3 cm as adenomas, since only 3 of 65 tumors of this size in my series had formed metastases In my experience they were all incidental findings at autopsy, since they are too small to produce renal symptoms Macroscopically they are sharply circumscribed and exhibit a yellowish or whitish color Histologically they are usually composed of solid cords of cells with sharp cell boundaries (Figs 117 and 118) The cytoplasm of the cells may be clear, dark or intermediate Mitoses are infrequent

but may be observed Growth is less active and there is little or no necrosis or hemorrhage but otherwise there is a close structural resemblance between these small tumors and the large malignant growths Since the solid adenomas appear to be small carcinomas I shall discuss them with the carcinomas

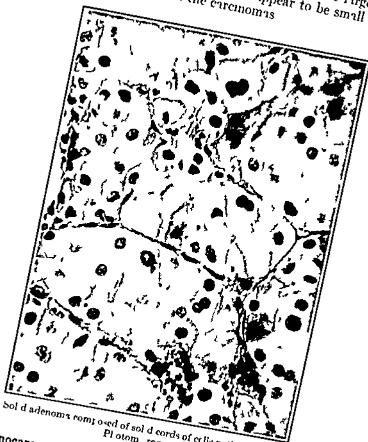


Fig 118 Solid adenoma composed of solid cords of cells with fairly clear cytoplasm Photomicrograph

2 **Adenocarcinoma of the Cortex (Hypernephroma).**—The term hypernephroma is ill chosen since it implies that the growth is of adrenal origin Its usage dates from the work of Grawitz who noted that the tumors are composed of clear cells resembling the foamy cells of the adrenal cortex and suggested that they develop from adrenal rests in the kidneys However it has been well established that these tumors develop from renal tissue and not from adrenal rests Some of them contain well formed tubules composed of dark cells and the majority show a cystadenomatous structure Tumor of known adrenal origin do not contain glands or cysts and are not composed of clear cells Adrenal tumors in young women produce virilism but no renal tumor has ever brot

about masculinization In spite of its inaccuracy "hypernephroma" is so firmly implanted in medical literature that it seems impossible to replace it with the more appropriate "adenocarcinoma"

The terms "Grawitz tumor" "hypernephroma" and "carcinoma" all refer to the same neoplasm which is in fact an adenocarcinoma of the kidney Adenocarcinoma includes all malignant renal neoplasms except the carcinomas of the renal pelvis the Wilms tumors and a few sarcomas The percentage of malignant renal tumors belonging to this group varies from 75 to 91 per cent in different reports In our autopsies 88 per cent of the malignant tumors are adenocarcinomas if cortical tumors over 3 cm in diameter are classified as malignant but the percentage is smaller if only those producing symptoms are regarded as malignant (Table 69)

Age Distribution Priestley found the peak incidence of adenocarcinoma in the sixth decade The distribution by decades in our autopsies is shown in Table 69 The maximum incidence is

TABLE 69 AGE DISTRIBUTION OF RENAL TUMORS

Age years	Adenocarcinoma 3 cm or larger	Solitary adenoma less than 3 cm	Wilms tumors	Pelvic epithelial tumors	Total
0–10	0	0	14	0	14
10–20	0	0	1	0	1
20–30	3	0	0	1	4
30–40	[illegible]	1	0	1	9
40–50	4	[illegible]	0	1	11
50–60	11	13	[illegible]	6	8[illegible]
60–70	82	20	3	1	33
70–80	70	13	0	3	9
80–100	20	[illegible]	0	[illegible]	[illegible]
Total	[illegible]	6[illegible]	18	18	173

in the seventh decade The youngest patient was a woman aged twenty-three years and there were only three persons under thirty years of age Over 90 per cent were in persons over forty years of age There is some doubt whether adenocarcinoma of the adult type ever occurs in children There were none in our autopsies and Ladd found none There are reports in the literature of hypernephroma in children but the histologic descriptions are not convincing Hellstrom described a hypernephroma in a child aged eighteen months but gave no microscopic illustrations

It will be noted in Table 69 that the tumors of the first decade are all of the Wilms type and that there are practically no renal tumors in the second and third decades

Sex All observers agree that adenocarcinoma is much more frequent in males In a large group Priestley found males 69.9 per cent females 30.1 per cent In our autopsies there were 248 males and 89 females with adenocarcinoma or small solid adenoma

This gives an incidence of about 1 *per cent in males and* 0 75 per cent in females

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in 37 per cent and tumor in *13 6* per cent Hematuria occurred at some time in 69 per cent and *tumor in 80 per cent But frequently* the initial symptoms do not suggest a renal neoplasm *In 38 of 9*? cases (41 per cent) Creevy found the initial symptoms misleading The presenting symptoms may *be due to metastases*



Fig 119 Adenoca c noma of the k dney Photograph

in a bone the brain *the lungs the neck or other situation In one of* our cases the pre enting symptom was a pathologic fracture of the tibia and in another the patient had symptoms of carcinoma of the lung but a bronchial biopsy revealed a hypernephroma Not uncommonly there is anemia and loss of weight with no symptoms referable to the kidneys *Occasionally there is an intermittent or* continuous fever suggesting an infectious disease

A plain roentgenogram may reveal an enlarged kidney A pyelogram *is usually necessary to establish the diagnosis Among* the features of the pyelogram are narrowing and distortion of the pelvis elongation of one or more calices obliteration of one or more *calices and abnormal position of the pelvis*

Pathology Tumors of moderate size appear usually as large spherical masses occupying either pole or the central portion of the kidney (Fig 119) Creevy described a tumor only 3 cm in

diameter which was deeply placed in the parenchyma and had eroded the pelvis causing hematuria. On section yellowish, whitish or hemorrhagic areas may be seen. The larger the tumor the more extensive is the necrosis and hemorrhage. The smaller tumors are still within the capsule of the kidney but the large growths penetrate the capsule and invade the surrounding tissue. The tumors frequently invade the renal vein and may extend through the vena cava to the right heart. Some tumors infiltrate the surrounding tissues to such an extent that they become inoperable without having formed metastases. Untreated tumors grow to very large dimensions. One hundred-eighteen of our 272 tumors were over 10 cm in diameter at the time of death, some were over 20 cm in diameter, and the maximum weight of the primary growth in our series was 3300 gm.

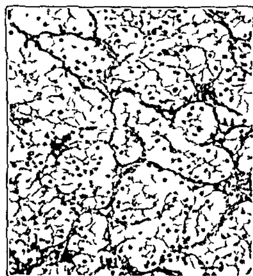


Fig. 1[illegible]0. Adenocarcinoma of the kidney showing solid alveoli of clear cells. Photomicrograph.

Table [illegible]0.—Relation of the Size of the Tumor to the Presence of Metastases in the Adenoma-Carcinoma Group

Diameter	Metastases	No metastases
Below 3 cm	3	6
3–4 cm	[illegible]	[illegible]
4–5 cm	[illegible]	16
5–6 cm	9	10
6–10 cm	[illegible]	[illegible]
Over 10 cm	100	18
Total	181	[illegible]

Metastases.—The relation of the size of the tumor to the presence of metastases is shown in Table 70. In the group under 3 cm. in diameter ...

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Metastases had formed from 13 of 119 tumors (11 per cent) less than 5 cm. in diameter but 100 of 118 tumors (85 per cent) over 10 cm. in diameter had metastases.



Fig. 191. Metastatic hypernephroma showing differentiation into dark cell tubule. Photomicrograph.

It is clear that there is no sharp separation between solid adenoma and hypernephroma with respect to size or the presence of metastases. Metastases seldom form before the tumor has attained a diameter of 5 cm. but tumors of small dimensions seldom cause symptoms and therefore do not come to clinical attention.

In 181 cases with metastases there were metastases in the lungs in 97, the liver in 78, the lymph nodes in 67, the bones in 51, the peritoneum in 23, the opposite kidney in 30, the adrenals in 33, the brain in 18, the heart in 13, the spleen in 3, the ovary in 3, the pancreas in 3, the skin in 2, and the thyroid in 1. The number in the

bones is probably underestimated since bones are not all thoroughly examined at postmortem. In 22 cases there was a tumor mass extending through the renal vein into the vena cava and in 4 of these it penetrated into the right atrium.

In view of the fact that the opposite kidney contained metastases in 30 of 181 cases one should hesitate to accept reports of bilateral hypernephroma in the sense of two independent neoplasms.



Fig. 122. Metastasis of an adenocarcinoma showing dark round cells without alveolar or tubular arrangement. Photomicrograph.

Microscopic Structure. The most frequent microscopic appearance is solid alveoli of clear cells (Fig. 120) but the clear cells may also be arranged in the form of papillary cysts or tubules. One may also find dark cells arranged in solid alveoli, papillary cysts or tubules (Fig. 121). Clear and dark cells may also be intermixed in alveoli or tubules. The most undifferentiated portions of malignant tumors are composed of dark rounded cells without alveolar or tubular arrangement (Fig. 122).

Cahill states that tumors composed entirely of clear cells afford a much better prognosis than those composed of dark granular cells or of both clear and dark cells.

It is usually impossible to establish the diagnosis of hypernephroma from examination of a metastasis unless the growth is composed of the typical large clear cells The clear structure is largely due to hydropic changes in the cytoplasm to a less extent to ac-

stood

Treatment It is generally agreed that nephrectomy should be performed as soon as the diagnosis is established provided that there are no demonstrable metastases In about one-half of those with metastases the lungs are involved and these metastases are demonstrable in roentgenograms If there be a solitary bone metastasis it is advisable to remove it as well as the kidney, since patients have been known to survive for many years after this procedure A solitary bone metastasis which develops many years after nephrectomy should be removed for the same reason Barney and Churchill reported an unusual example of what may be accomplished by removal of a metastatic growth Their patient, a woman fifty five years of age had a demonstrable pulmonary metastasis at the time of the nephrectomy Fifteen months after the nephrectomy a lobectomy was performed The patient was in good health five years after the lobectomy One of our patients survived for two years after removal of the affected kidney and a metastatic growth in the brain

Prognosis The most extensive follow up records have been published by Priestley Of 502 adenocarcinomas 47 7 per cent survived over three years 38 4 per cent over five years and 27 3 per cent over ten years In the absence of demonstrable metastases the outcome depends to a large extent upon the size of the tumor and the degree of extension into the perirenal connective tissue Some patients are cured when there is extension into the renal vein

In 36 of our cases nephrectomy was performed The periods of survival after nephrectomy are as follows less than six months 6 six months to one year 7 one to two years 3 two to five years 5 five to ten years 3 ten to fifteen years 1 and seventeen years 1 At autopsy there were metastases in 25 of the 26 cases but one patient who survived nephrectomy nine years showed no metastases

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C WILMS TUMORS

Practically the only malignant renal tumor of children is an embryonal mixed growth usually called Wilms tumor Nearly all of these tumors are found in children under ten years of age and over 90 per cent appear before the age of seven years but an occasional adult renal tumor is of the Wilms type Sparks found 26 reports in the literature of Wilms tumors in adults and 3 of our 18 cases were in persons over fifty years old (Table 71) There is no sex predisposition and the right and left kidneys are involved with equal frequency

The tumor apparently develops from vestigial embryonic renal *tissue Since many tumors contain striated muscle Wilms postu*

TABLE 71 WILMS TUMORS

Autopsy number	Age years	Sex	Blood pressure	Side	Size	Metastases	Histology
20-19	1 5	F		L	34 x [illegible]0 cm	0	Rhabdomyosarcoma
22 413	8	F		L	6000 gm	0	Rhabdomyosarcoma
27 1058	4	F		R	1000 gm	Vena cava right atrium	Adenosarcoma
27 1306	6	F		R	Very large	Vena cava liver nodes	Adenosarcoma
30-1026	1 5	F		R	Very large	lungs nodes [illegible]	Adenosarcoma
31 1080	58	F	130 84	R	large	Liver	Adenosarcoma
36-[illegible]20	64	M	110 [illegible]	L	1750 gm	Vena cava	Rhabdomyosarcoma
40 [illegible]270	5	M	130 80	L	860 gm	Brain lungs	Adenosarcoma
38 2558	7 mo	M		R	6 x [illegible] cm	[illegible]	Adenosarcoma
39-35	1 5	M		L		0	Adenosarcoma
41-419	4	M	150 [illegible]	L	300 gm	lungs	Adenosarcoma
41 [illegible]	12	M	110 80	L	4 x 10 cm	[illegible] lungs nodes [illegible]	Adenosarcoma
42 10[illegible]	2	F		R	700 gm	0	Adenosarcoma
45-4		M		R	85 gm	[illegible] nodes lungs	Adenosarcoma
45 1334	4	F	108 [illegible]0	L R	L [illegible] cm R 9 cm	Liver lungs nodes	Adenosarcoma
46-56	8 mo	M		R	8 x 7 cm	brain	Adenosarcoma
46-1051	10 mo	M	300 [illegible]	L	10 cm	None	Adenosarcoma (glomerulonephritis)
47 04	[illegible] 5	M	168,130	L	[illegible] x 5 cm	None	Adenosarcoma (glomerulonephritis)

lated that a portion of the myotome becomes displaced into the renal blastema, but the renal blastema is composed of rather primitive mesenchymal cells and it is easily possible that they retain multipotential properties

In over 80 per cent of the patients the first symptom is enlargement of the kidney, but occasionally hematuria or pain is the initial sign of the disease The tumor grows rapidly producing a marked enlargement of the abdomen, cachexia and death usually



Fig 123 — Wilms tumor—adenosarcoma Note the tubules and the undifferentiated mesenchymal tissue Photomicrograph

within a few months In the differential clinical diagnosis unilateral hydronephrosis must be considered since this may produce a massive enlargement of the kidney

The tumor progresses at first by expansive growth and usually attains an enormous size One or both poles of the kidney may usually be found as a cap on the cranial or caudal ends of the tumor The growth soon infiltrates through the capsule into the perirenal connective tissue, and it also invades the veins and lymphatics to produce distant metastases Metastases develop most frequently in the lungs, liver and regional lymph nodes, but they may form in the brain, adrenals or other organs

Microscopically about two-thirds of the tumors have the structure of adenosarcoma (Fig 123) There are areas of cellular mesenchymal tissue which may be solid or may exhibit stages in the differentiation of tubules Some well formed tubules are seen and

one may find all stages from solid mesenchyma to complete tubules. The tumor reproduces the appearances seen when the normal renal blastema develops into tubules except that no complete glomeruli are formed. In about one-third of the tumors a more complex structure is encountered. In addition to areas of adeno-sarcoma there are masses of striated muscle and less frequently smooth muscle and cartilage. Occasionally the growth consists almost entirely of striated muscle fibers in different stages of development: rhabdomyosarcoma. In view of the varying histological structure the simple designation of Wilms tumor is convenient. No differences in the clinical behavior of the different histological varieties have been established.

Treatment and Prognosis. Some surgeons believe that nephrectomy should be done without delay (Ladd). Others give heavy irradiation and perform nephrectomy four to six weeks later. When the tumor is radiosensitive it decreases in size remarkably and nephrectomy is much easier. But some tumors are radioresistant (Kretschmer) and continue to increase in size during the irradiation.

McNeill and Chilko reviewed the literature with respect to the prognosis and found that over 90 per cent of the patients succumb to the disease. Priestley and Schulte reported 6 of 59 patients well over five years. Some observers report no cures. Ladd found that the great majority of recurrences take place within two years after the operation. A patient free of symptoms at the end of two years has a good chance of cure. Maslow found 3 cases of Wilms tumor and probably a fourth in one family.

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D. TUMORS OF THE RENAL PELVIS

The epithelial tumors arising from the renal pelvis may be arranged into 3 groups: Papilloma, papillary carcinoma and flat transitional or squamous cell carcinoma.

(a) **Papilloma** —Papillomas may develop in the urinary bladder ureter or renal pelvis They are much more frequent *in the bladder* than in the upper urinary tract They are often multiple and pelvic papillomas may be found in association with papillomas of the bladder In the pelvis they may be single or multiple Hematuria is nearly always present and usually a deformity is demonstrable in the pyelogram The growth is of cauliflower shape and is attached to the mucosa by a narrow pedicle In our autopsies there were two examples of papilloma—the one a small papilloma in an upper calyx the other a massive papilloma involving the upper half of the kidney

(b) **Carcinoma** —Among 318 renal tumors removed at the Mayo Clinic Hunt found 23 pelvic carcinomas (7 2 per cent) Of these 8 were sessile and 15 papillary In our autopsies there were 272 hypernephromas over 3 cm in diameter and 18 malignant pelvic tumors (6 2 per cent) *Papillary carcinomas* are difficult to separate sharply from benign papillomas and more of these tumors are classified as malignant by some pathologists than by others If the tumor has formed metastases or invaded the kidney it should be called a [illegible] extension down the

[illegible] ιalignant They are composed of cords and masses of transitional epithelium which is sometimes of epidermoid structure or cornified Many of these tumors are definite squamous cell carcinomas The tumor invades the kidney at first and then the perirenal tissues Metastases are found in the liver regional lymph nodes lungs and other organs Twelve of our malignant epithelial tumors of the pelvis were flat infiltrating squamous cell carcinomas and 6 were papillary carcinomas All had formed extensive metastases Several observers stress the relation between calculi leukoplakia and squamous cell carcinoma (Scholl and Foulds Patch)

The prognosis of squamous cell carcinoma is poor Hunt reported no cures from nephrectomy in his 8 cases There are a few cures of papillary carcinoma

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